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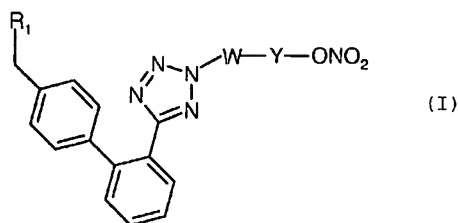
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(54) Title: NITROOXY SARTAN DERIVATIVES AS ANGIOTENSIN II RECEPTOR BLOCKERS FOR THE TREATMENT OF CARDIOVASCULAR AND INFLAMMATORY DISEASES



(I)

(57) Abstract: Angiotensin II receptor blockers nitroderivatives of formula (I) having wider pharmacological activity and enhanced tolerability. They can be employed for treatment cardiovascular and renal diseases and inflammatory processes.

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NITROOXY SARTAN DERIVATIVES AS ANGIOTENSIN II RECEPTOR BLOCKERS FOR THE
TREATMENT OF CARDIOVASCULAR AND INFLAMMATORY DISEASES

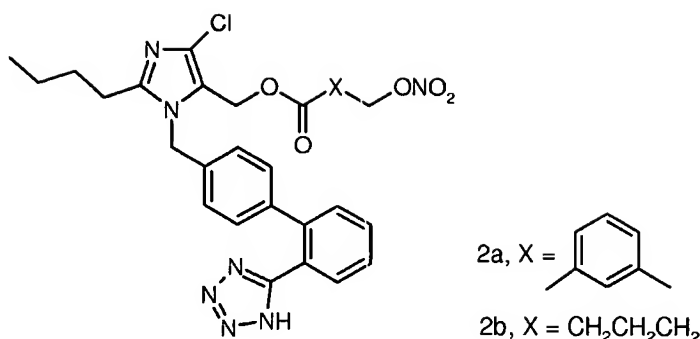
The present invention relates to Angiotensin II
5 Receptor Blocker (ARB) nitroderivatives, pharmaceutical
compositions containing them and their use for the
treatment of cardiovascular, renal and chronic liver
diseases, inflammatory processes and metabolic syndromes.

With the angiotensin II receptor blockers a class of
10 compounds is intended, comprising as main components
Losartan, EXP3174, Exp3179, Dup532, Candesartan,
Tasosartan, Valsartan, Elisartan, Irbesartan and Olmesartan
Olmesartan medoxomil.

ARBs are approved only for the treatment of
15 hypertension, the antihypertensive activity is due mainly
to selective blockade of AT₁ receptors and the consequent
reduced pressor effect of angiotensin II. Angiotensin II
stimulates the synthesis and secretion of aldosterone and
raises blood pressure via a potent direct vasoconstrictor
20 effect.

Now, it has been reported that angiotensin II receptor
blockers have side-effects such as for example hypotension,
hyperkalaemia, myalgia, respiratory-tract disorders, renal
disorders, back pain, gastrointestinal disturbances,
25 fatigue, and neutropenia (Martindale, Thirty-third edition,
p. 921).

Maria C. Breschi et al., in Journal of Medicinal
Chemistry, 47 (23), 5597-5600, 2004, describes two NO-
releasing Losartan of formulae 2a and 2b



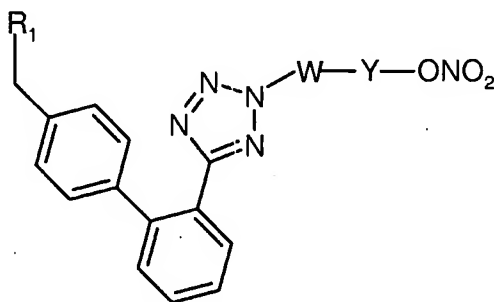
and the results of an "exploratory" in vivo protocol evaluating the antihypertensive action of the compound of formula 2a in comparison with the "native" sartan and a
 5 ACE inhibitor (i.e. captopril). In this test all the compounds had shown practically equivalent effect on the reduction of the systolic blood pressure.

It was now object of the present invention to provide
 10 a new class of Angiotensin II Receptor Blocker nitroderivatives having an improved pharmacological activity an improved pharmacodynamic and pharmacokinetic profiles as compared to the compounds of the prior art. It has been so surprisingly found that angiotensin II receptor
 15 blocker nitroderivatives of the invention have a significantly improved overall profile as compared to native compounds both in term of wider pharmacological activity and enhanced tolerability.

In particular, it has been recognized that the
 20 angiotensin II receptor blocker nitroderivatives of the present invention exhibit a strong anti-inflammatory, antithrombotic and antiplatelet activity and can be furthermore employed for treating or preventing heart failure, myocardial infarction, ischemic stroke,
 25 atherosclerosis, ocular and pulmonary hypertension, hypertension, diabetic nephropathy, peripheral vascular diseases, left ventricular dysfunction and hypertrophy,

liver fibrosis, portal hypertension and metabolic syndromes.

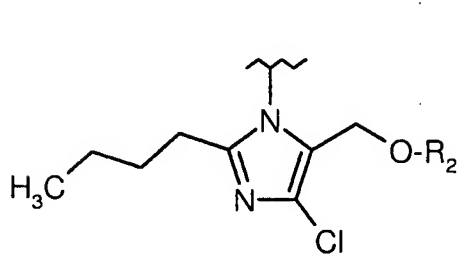
Object of the present invention are, therefore, Angiotensin II Receptor Blocker nitroderivatives of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof:



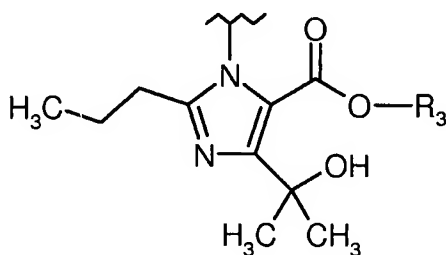
(I)

wherein:

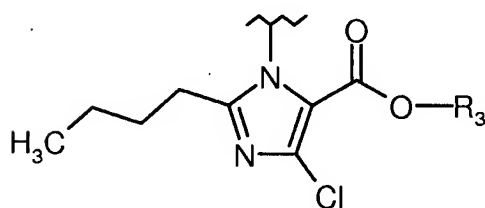
10 R_1 is selected from the group consisting of:



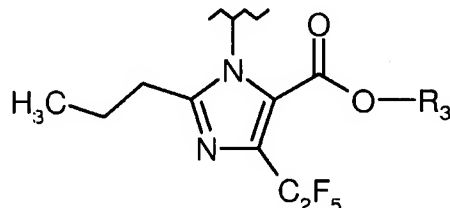
(Ia)



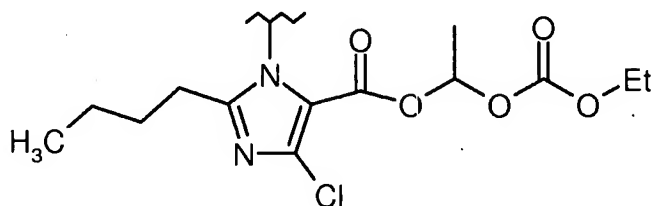
(Ib)



(Ic)

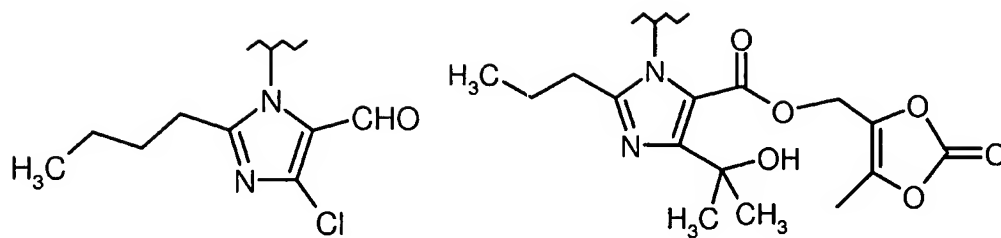


(Id)

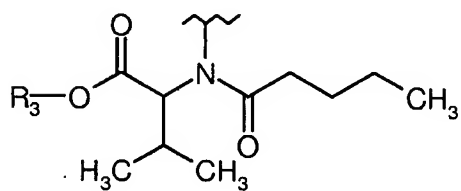


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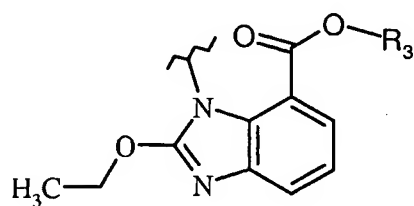
(Ie)



(If)

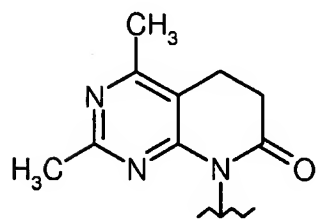


(Ig)

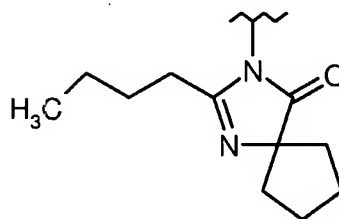


5

(Ih)

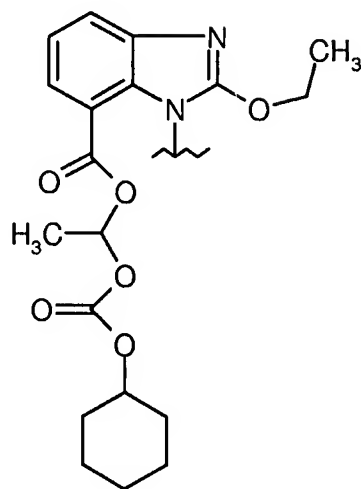


(Ii)



(Il)

(Im)



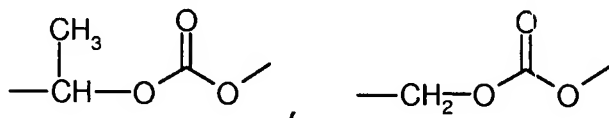
(In)

10 wherein

R_2 is H, or $-W_1-Y_0-ONO_2$ wherein W_1 is
 $-C(O)-$ or $-C(O)O-$;

Y_0 is as reported below;

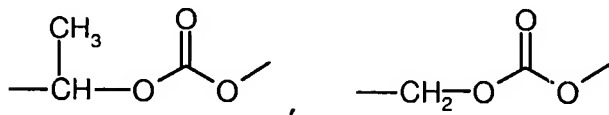
R_3 is H, $-Y_0-ONO_2$ or $-W_2-Y_0-ONO_2$, wherein W_2 is



Y_0 is as reported below;

5 W has the following meanings:

$-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$,



preferably in the radical R_1 of formula (Ia) when R_2 is $-W_1-Y_0-ONO_2$, W_1 is $-\text{C}(\text{O})-$;

10 preferably in the radical R_1 of formula (Ib), (Ic), (Id), (Ih) or (Ii), R_3 is $-Y_0-ONO_2$;

more preferably when R_1 is (Ia), R_2 is H or when R_1 is chosen among the radicals of formula (Ib), (Ic), (Id), (Ih) or (Ii), R_3 is H;

15 Y and Y_0 are the same or different and are bivalent radicals having the following meanings:

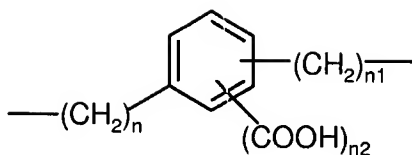
a)

- straight or branched C_1-C_{20} alkylene, preferably C_1-C_{10} alkylene, more preferably C_3-C_6 alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T_0 , wherein T_0 is

$-\text{OC}(\text{O})-(C_1-C_{10} \text{ alkyl})-ONO_2$ or $-\text{O}-(C_1-C_{10} \text{ alkyl})-ONO_2$;

- cycloalkylene having from 5 to 7 carbon atoms, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably T is CH_3 ;

b)



wherein

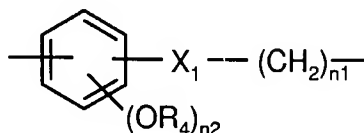
n is an integer from 0 to 20, preferably n is 0 or 1,

n1 is an integer from 1 to 20, preferably n1 is an integer

5 from 1 to 6, more preferably n1 is 1,

n2 is 0 or 1, preferably n2 is 0;

c)



wherein:

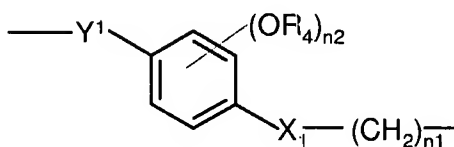
10 n1 is an integer from 1 to 20, preferably n1 is an integer from 1 to 6,

n2 is 0 or 1,

X1 is $-(CH_2)_3-OC(O)-$ or $-CH=CH-C(O)O-$, and

R4 is H or CH3;

15 d)



wherein:

20 n1 is an integer from 1 to 20, preferably n1 is an integer from 1 to 6,

n2 is 0 or 1;

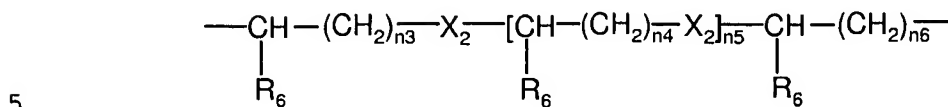
X1 is $-OC(O)-$, $-C(O)O-$,

Y1 is $-CH=CH-$, $-(CH_2)_3-$, and

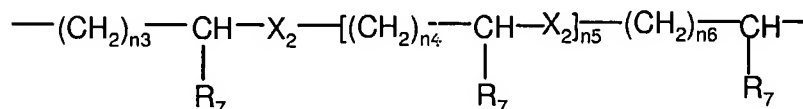
R4 is H or CH3;

when Y or Y₀ are selected from the bivalent radicals of the groups b), c) or d) the -ONO₂ group is linked to -(CH₂)_{n1}- group;

g)



h)



wherein X₂ is O or S,

n₃, n₄ and n₆ are integer independently selected from 0 to 20, preferably n₃, n₄ and n₆ are selected from 1 to 5, more preferably n₃, n₄ and n₆ are 1,

n₅ is an integer from 0 to 6, preferably from 0 to 4, more preferably n₅ is 0,

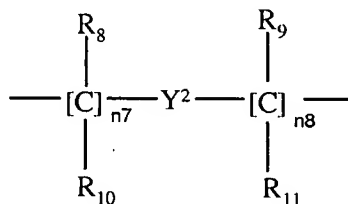
R₆ is H, CH₃ or nitrooxy group, preferably R₆ is H,

R₇ is CH₃ or nitrooxy group;

when Y or Y₀ are selected from the bivalent radicals of the group g) the -ONO₂ group is linked to -(CH₂)_{n6}- group;

when Y or Y₀ are selected from the bivalent radicals of the group h) the -ONO₂ group is linked to -CH(R₇)- group;

i)



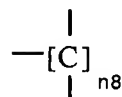
wherein:

n₇ is an integer from 0 to 10;

n₈ is an integer from 1 to 10;

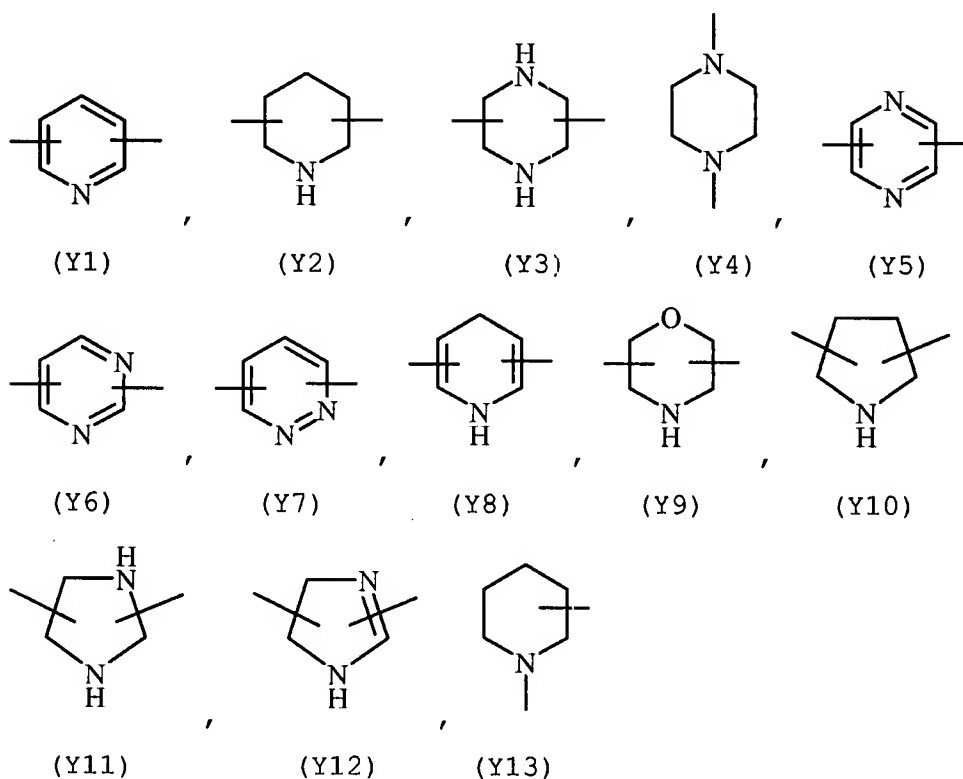
R₈, R₉, R₁₀, R₁₁ are the same or different, and are H or straight or branched C₁-C₄ alkyl, preferably R₈, R₉, R₁₀, R₁₁ are H;

wherein the $-\text{ONO}_2$ group is linked to



wherein n8 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5
 5 or 6 members ring, containing one or more heteroatoms
 selected from nitrogen, oxygen, sulfur,
 and is selected from



The term " $\text{C}_1\text{-C}_{20}$ alkylene" as used herein refers to
 15 branched or straight $\text{C}_1\text{-C}_{20}$ saturated hydrocarbon chain that
 results from the removal of two hydrogen atoms from an
 acyclic saturated hydrocarbon, preferably having from 1 to
 10 carbon atoms such as $-\text{CH}_2-$, $-\text{CH}_2\text{-CH}_2-$, $-(\text{CH}_2)_3-$, $-(\text{CH}_2)_4-$,
 $-(\text{CH}_2)_5-$, $-(\text{CH}_2)_6-$ and the like.

20 The term " $\text{C}_1\text{-C}_{10}$ alkyl" as used herein refers to
 branched or straight chain alkyl groups comprising one to
 ten carbon atoms, including methyl, ethyl, n-propyl,

isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, n-octyl and the like.

The term "cycloalkylene" as used herein refers to ring having from 5 to 7 carbon atoms including, but not limited to, cyclopentylene, cyclohexylene optionally substituted with side chains such as straight or branched (C₁-C₁₀)-alkyl, preferably CH₃.

The term "heterocyclic" as used herein refers to saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, such as for example pyridine, pyrazine, pyrimidine, pyrrolidine, morpholine, imidazole and the like.

Another aspect of the present invention provides the use of the compounds of formula (I) in combination with at least a compound used to treat cardiovascular disease selected from the group consisting of: ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, calcium channel blockers, diuretics, antithrombotics such as aspirin, nitrosated ACE inhibitors, nitrosated HMGCoA reductase inhibitors, nitrosated beta-adrenergic blockers, nitrosated aspirin and nitrosated diuretics.

Suitable ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, calcium channel blockers, antithrombotics and diuretics are described in the literature such as The Merck Index (13th edition).

Suitable nitrosated compounds are disclosed in WO 98/21193, WO 97/16405 and WO 98/09948.

The administration of the compounds above reported can be carried out simultaneously or successively.

The present invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the compounds and/or compositions of the present

invention and one or more of the compounds used to treat cardiovascular diseases reported above.

As stated above, the invention includes also the pharmaceutically acceptable salts of the compounds of
5 formula (I) and stereoisomers thereof.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, triethylamine,
10 dibenzylamine, piperidine and other acceptable organic amines.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction
15 in an organic solvent such as acetonitrile, tetrahydrofuran with the corresponding organic or inorganic acids.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids. Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids.
20 Salts with nitric acid are preferred.

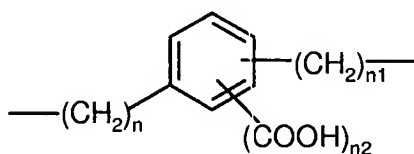
The compounds of the invention which have one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures,
25 racemates or racemate mixtures. Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

Preferred compounds are those of formula (I) wherein R_1 is (Ie), (If), (Ig), (Il), (Im), (In) or
30 R_1 is (Ia), (Ib), (Ic), (Id), (Ih), (Ic) wherein R_2 and R_3 are H,
W is as above reported, and
Y has the following meanings:

a)

- straight or branched C_1 - C_{20} alkylene, preferably C_1 - C_{10} , more preferably C_3 - C_6 alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-\text{ONO}_2$ or T_0 , wherein T_0 is
- $-\text{OC}(\text{O})-(C_1-C_{10} \text{ alkyl})-\text{ONO}_2$ or $-\text{O}-(C_1-C_{10} \text{ alkyl})-\text{ONO}_2$;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably T is CH_3 ;

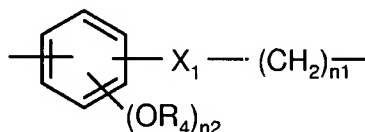
b)



wherein

- n is an integer from 0 to 20, preferably n is 0 or 1,
- $n1$ is an integer from 1 to 20, preferably $n1$ is an integer from 1 to 6, more preferably $n1$ is 1,
- $n2$ is 0 or 1, preferably $n2$ is 0;

c)

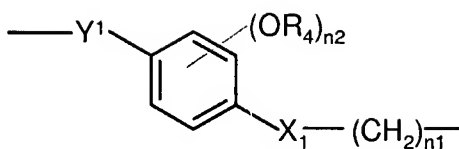


20

wherein:

- $n1$ is an integer from 1 to 20, preferably $n1$ is an integer from 1 to 6,
- $n2$ is 0 or 1;
- X_1 is $-(\text{CH}_2)_3-\text{OC}(\text{O})-$ or $-\text{CH}=\text{CH}-\text{C}(\text{O})\text{O}-$
- R_4 is H or CH_3 ;

d)



wherein:

n1 is an integer from 1 to 20, preferably n1 is an integer from 1 to 6,

5 n2 is 0 or 1;

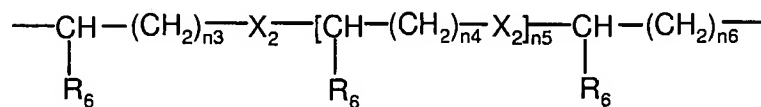
X₁ is -OC(O)-, -C(O)O-,

Y¹ is -CH=CH-, -(CH₂)₃-, and

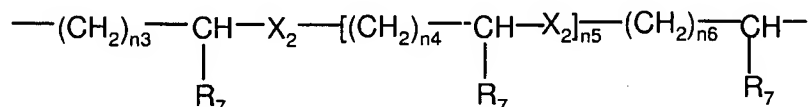
R₄ is H or CH₃;

when Y or Y₀ are selected from the bivalent radicals of the
10 groups b), c), d) the -ONO₂ group is linked to -(CH₂)ₙ₁-
group;

g)



15 h)



wherein X₂ is O or S,

n3, n4 and n6 are integer independently selected from 0 to
20, preferably n3, n4 and n6 are selected from 1 to 5, more
20 preferably n3, n4 and n6 are 1,

n5 is an integer from 0 to 6, preferably from 0 to 4, more
preferably n5 is 0,

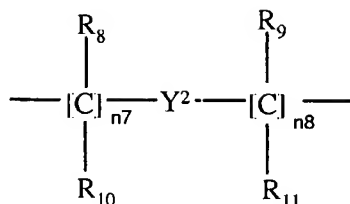
R₆ is H, CH₃ or nitrooxy group, preferably R₆ is H,

R₇ is CH₃ or nitrooxy group;

25 when Y or Y₀ are selected from the bivalent radicals of the
group g) the -ONO₂ group is linked to -(CH₂)ₙ₆- group;

when Y or Y₀ are selected from the bivalent radicals of the
group h) the -ONO₂ group is linked to -CH(R₇)-;

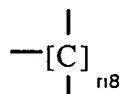
i)



wherein:

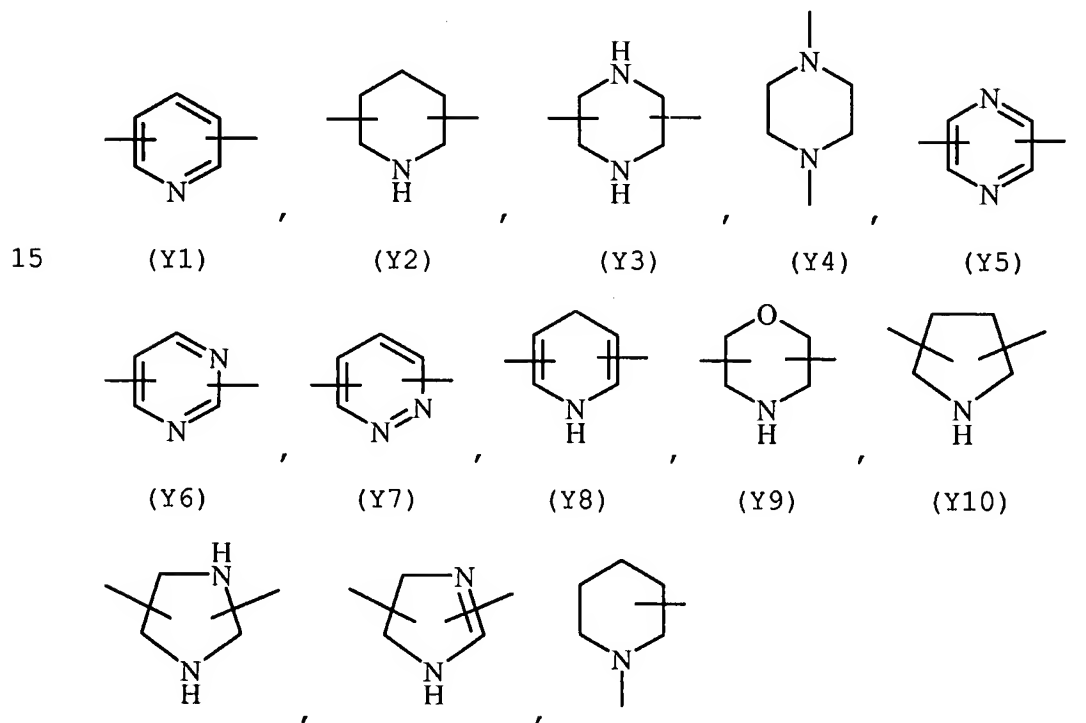
n7 is an integer from 0 to 10;

5 n8 is an integer from 1 to 10;

R₈ R₉, R₁₀, R₁₁ are H;wherein the -ONO₂ group is linked to

wherein n8 is as defined above;

- 10 Y² is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and is selected from



(Y11) (Y12) (Y13)

Another preferred compounds are those of formula (I) wherein

R_1 is (Ie), (If), (Ig), (Il), (Im), (In) or

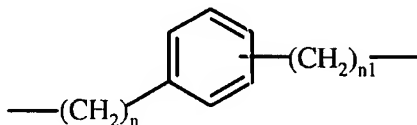
5 R_1 is (Ia), (Ib), (Ic), (Id), (Ih), (Ic) wherein R_2 and R_3 are H,

W is as above reported, and

Y has the following meanings:

a) straight C_1 - C_{10} alkylene, preferably C_3 - C_6 alkylene;

10 b)

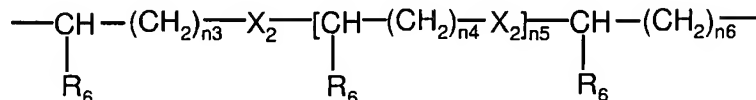


wherein

n is 0 or 1,

$n1$ is 1;

15 g)



wherein

X_2 is O or S,

$n3$, and $n6$ are selected from 1 to 5,

20 $n5$ is 0,

R_6 is H,

Another preferred compounds are those of formula (I) wherein

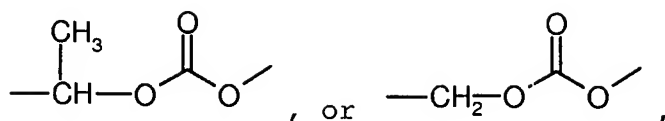
R_1 is the radical of formula (Ia), wherein

25 R_2 is $-W_1-Y_0-ONO_2$ wherein

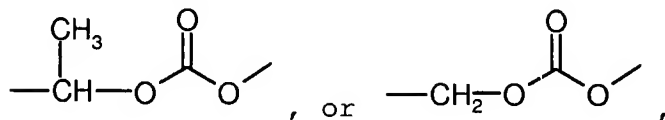
W_1 is $-C(O)-$ or $-C(O)O-$, preferably W_1 is $-C(O)-$

Y_0 is as defined below,

W is $-C(O)-$, $-C(O)O-$,



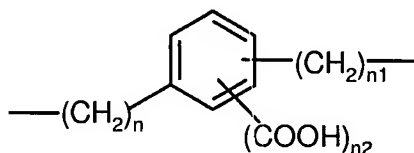
preferably W is



Y and Y₀ are the same or different and have the following
5 meanings:

a) straight C₁-C₁₀ alkylene, preferably C₃-C₆ alkylene;

b)



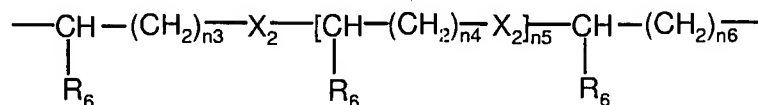
wherein

10 n is 0 or 1,

n₁ is 1,

n₂ is 0;

g)



15

wherein

X₂ is O or S,

n₃, and n₆ are selected from 1 to 5,

n₅ is 0,

20 R₆ is H,

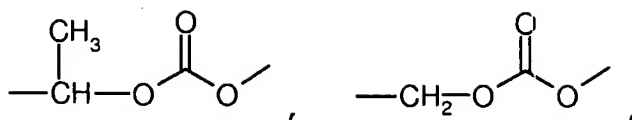
Another preferred group of compounds are those of
formula (I) wherein

R₁ is a radical of formula (Ib), (Ic), (Id), (Ih) or (Ii)

wherein

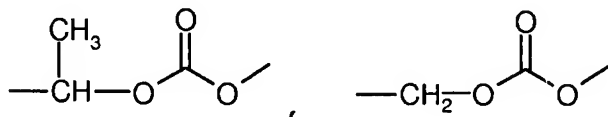
25 R₃ is -Y₀-ONO₂ or -W₂-Y₀-ONO₂ wherein

W₂ is

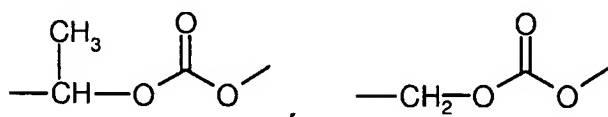


Y_0 is as defined below,

W is $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$



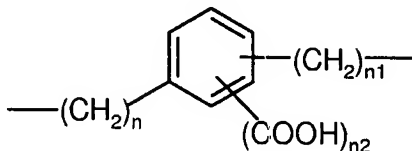
5 preferably W is



Y and Y_0 are the same or different and have the following meanings:

a) straight C_1 - C_{10} alkylene, preferably C_3 - C_6 alkylene;

10 b)



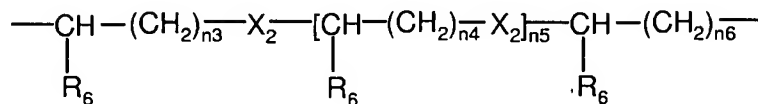
wherein

n is 0 or 1,

$n1$ is 1,

15 $n2$ is 0;

g)



wherein

20 X_2 is O or S,

$n3$, and $n6$ are selected from 1 to 5,

$n5$ is 0,

R_6 is H,

Another preferred group of compounds are those of formula (I) wherein

R_1 is a radical of formula (Ib), (Ic), (Id), (Ih) or (Ii) wherein

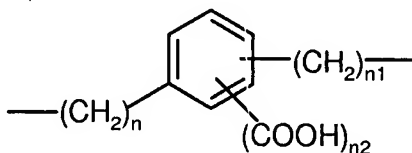
5 R_3 is $-Y_0-ONO_2$ wherein Y_0 is as defined below,

W is $-C(O)O-$

Y and Y_0 are the same or different and have the following meanings:

a) straight C_1-C_{10} alkylene, preferably C_3-C_6 alkylene;

10 b)



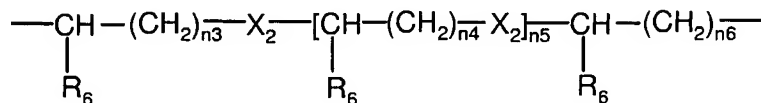
wherein

n is 0 or 1,

n1 is 1,

15 n2 is 0;

g)



wherein

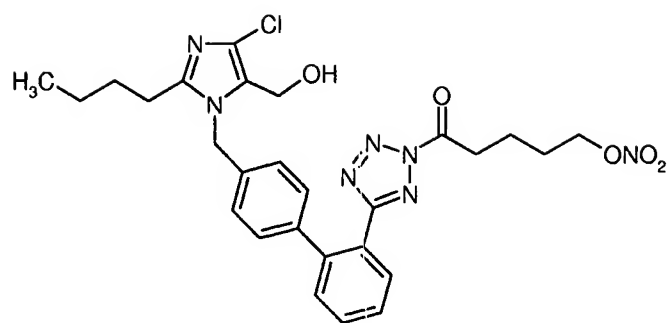
20 X_2 is O or S,

n3, and n6 are selected from 1 to 5,

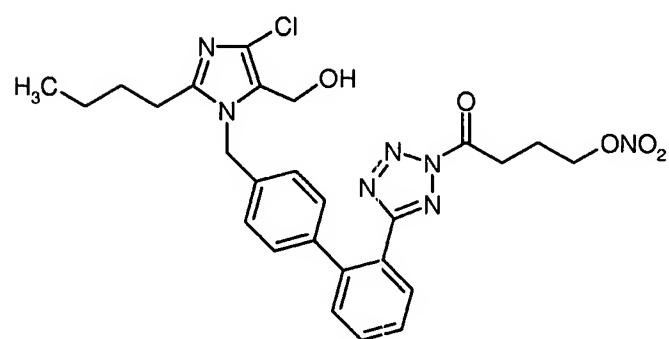
n5 is 0,

R_6 is H,

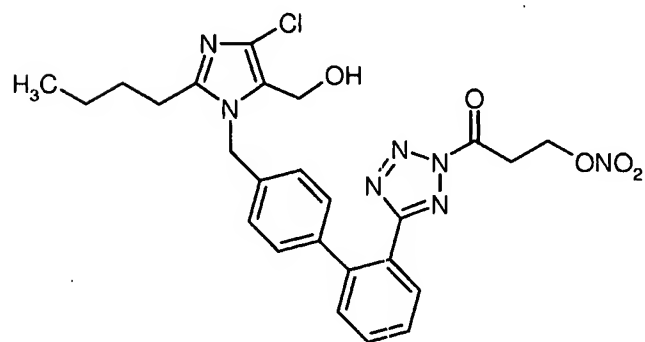
Most preferred compounds are



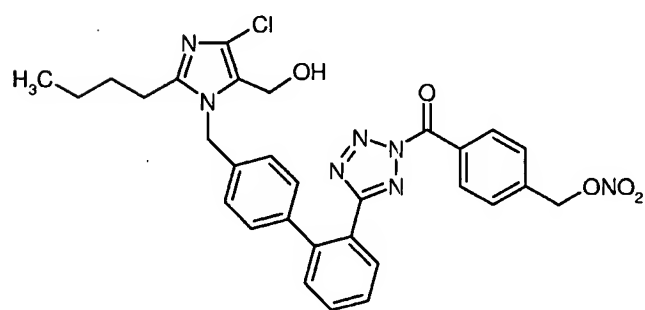
(1)



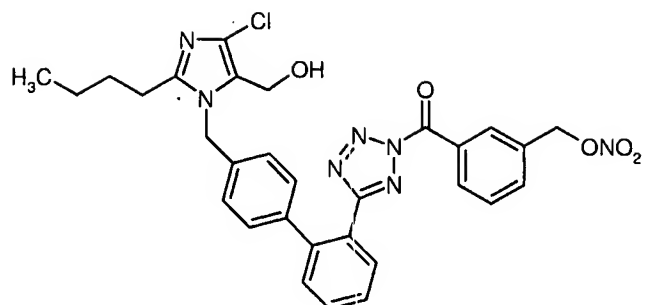
(2)



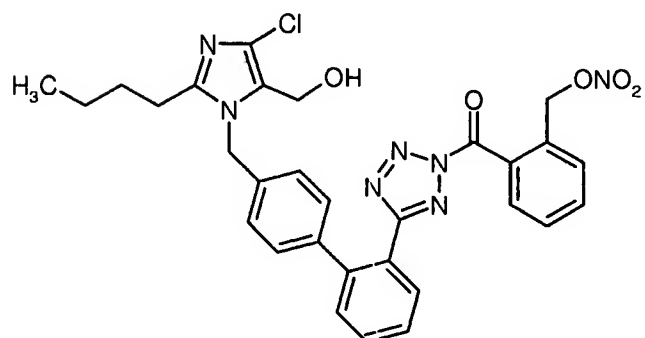
(3)



(4)

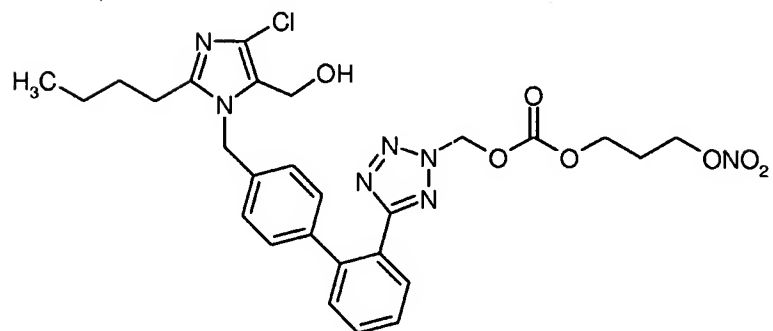


(5)

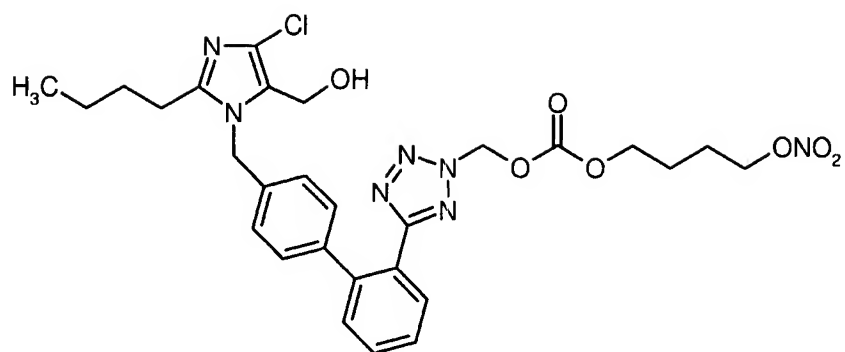


5

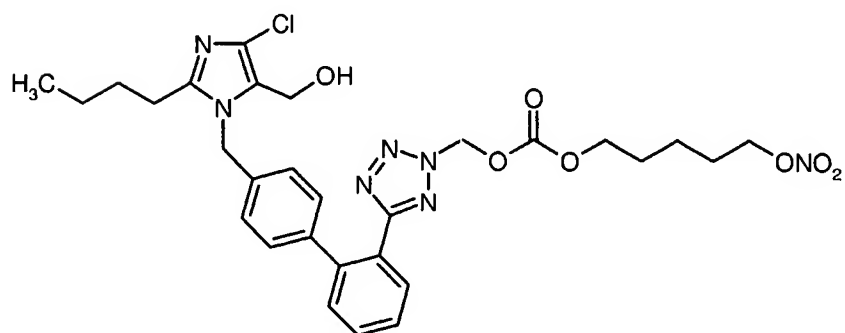
(6)



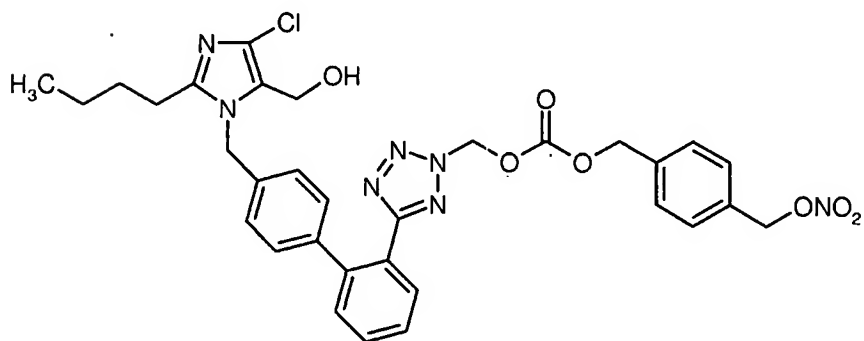
(7)



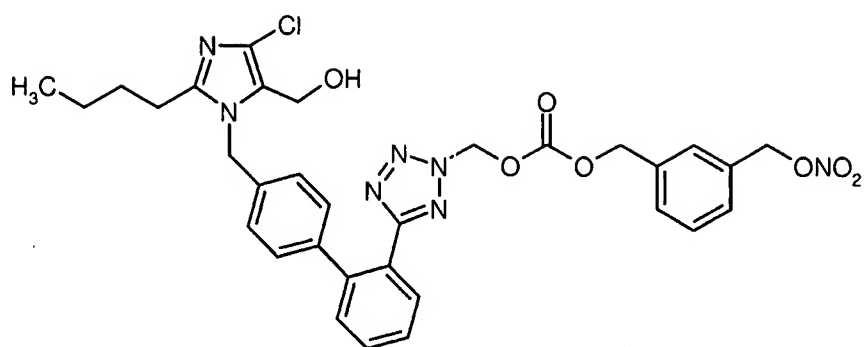
(8)



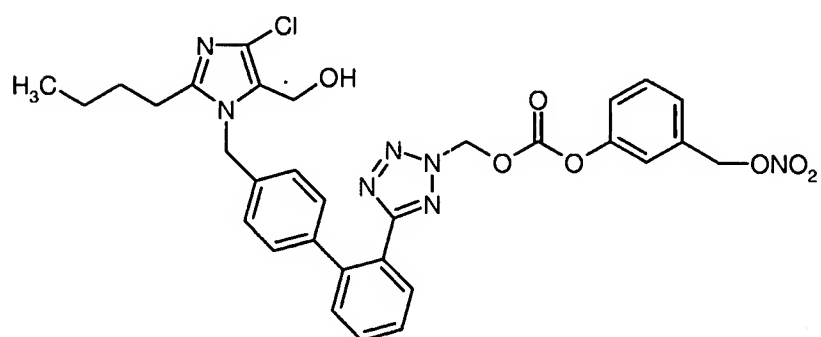
(9)



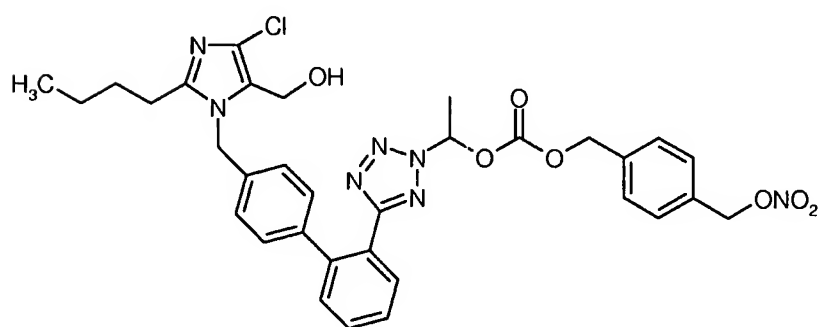
(10)



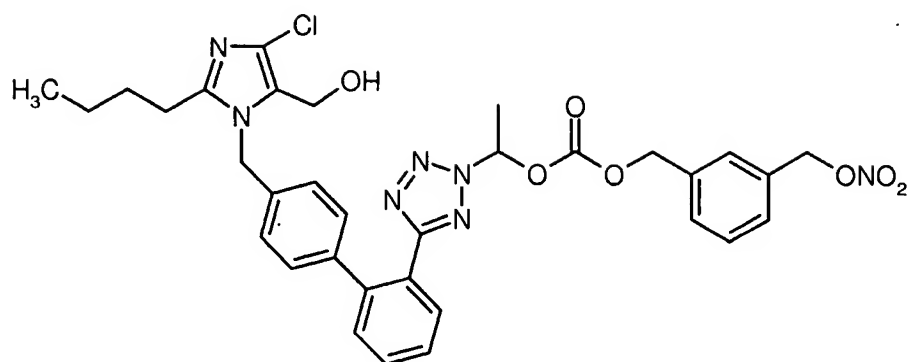
(11)



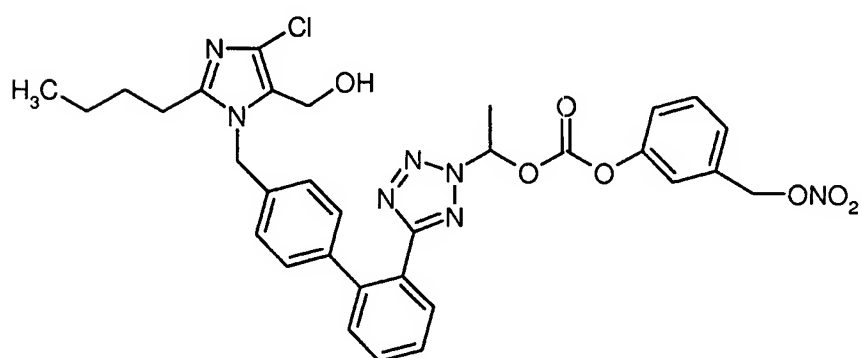
(12)



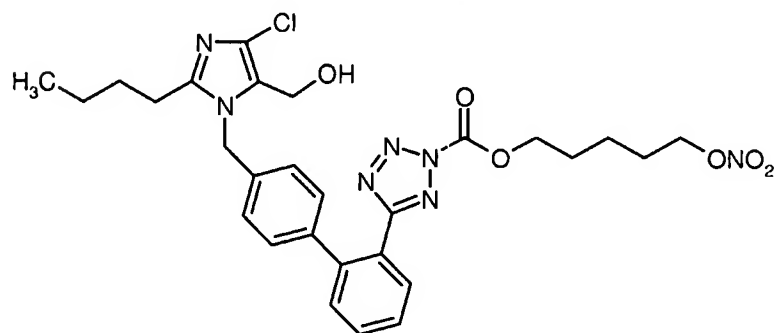
(13)



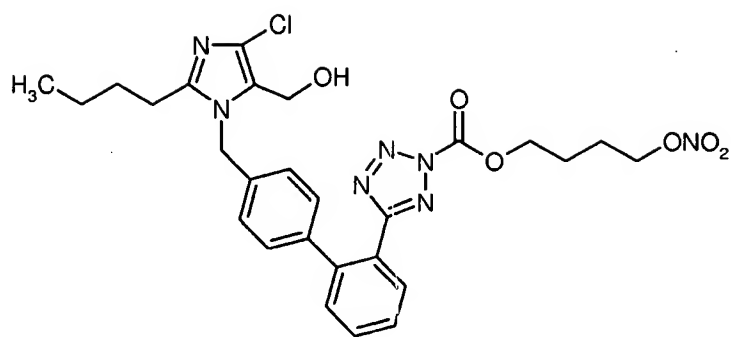
(14)



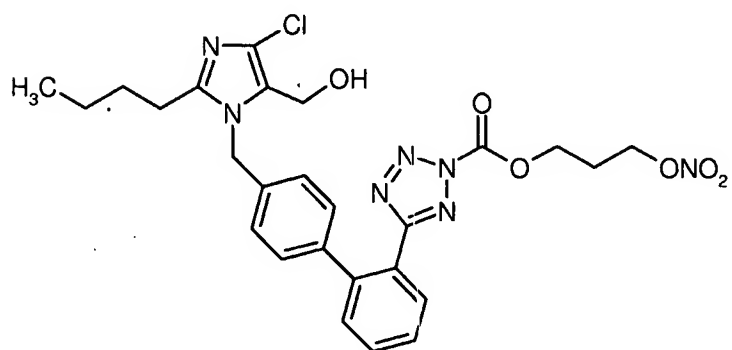
(15)



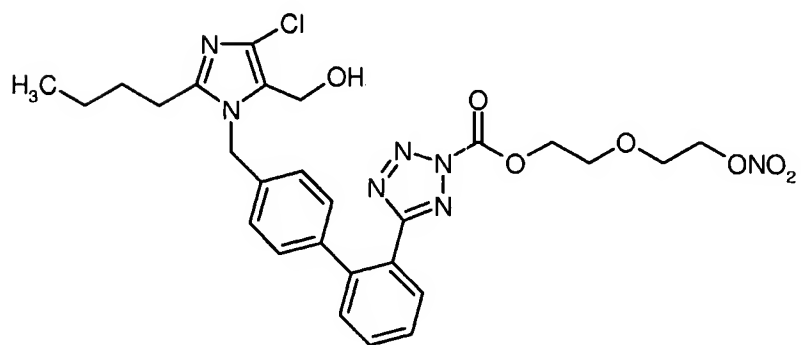
(16)



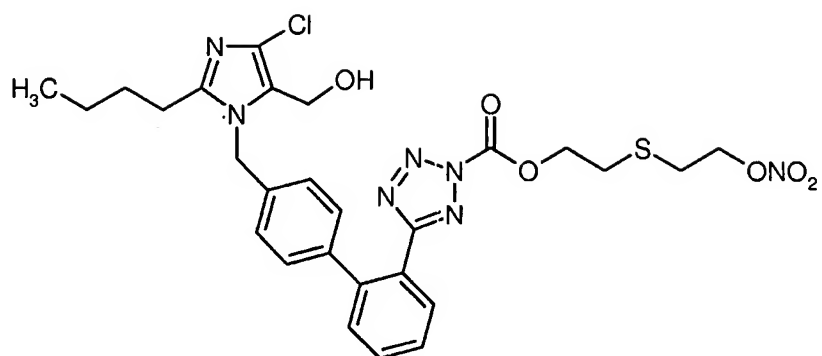
(17)



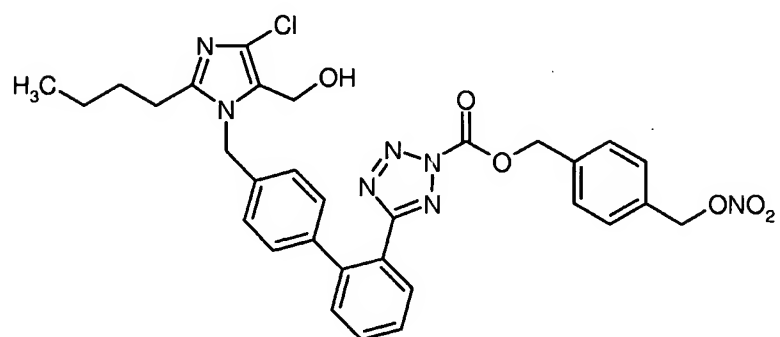
(18)



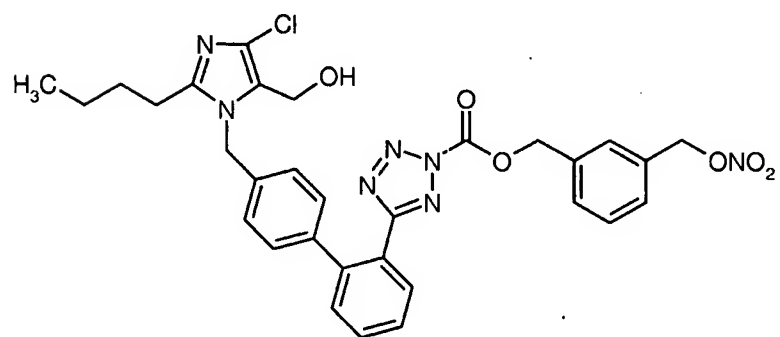
(19)



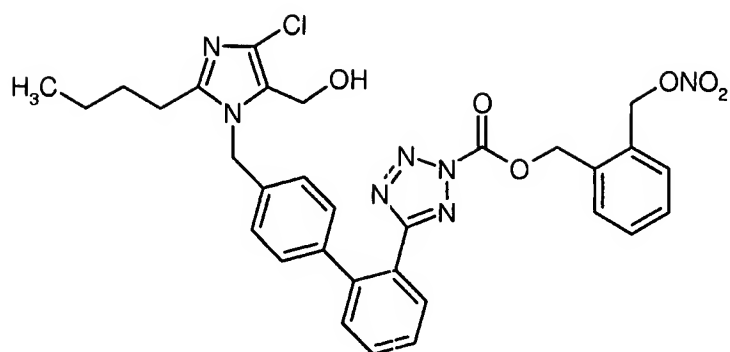
(20)



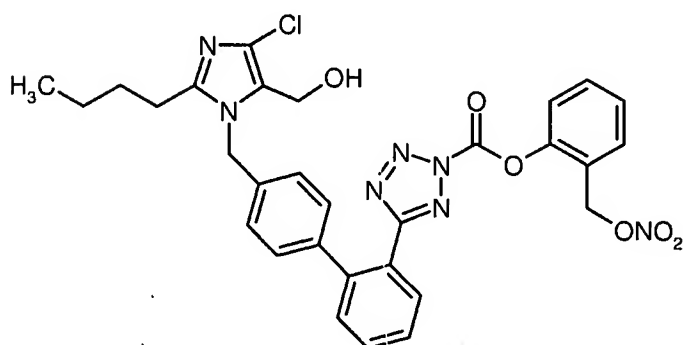
(21)



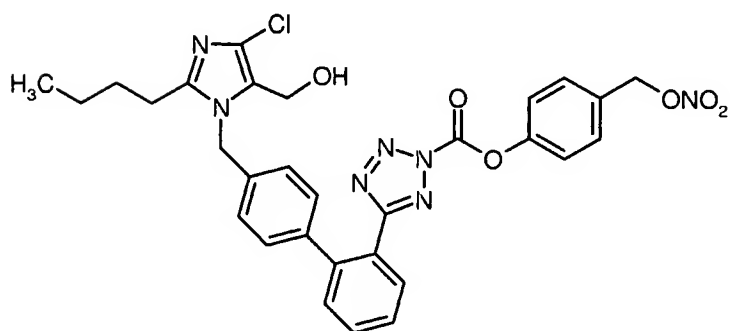
(22)



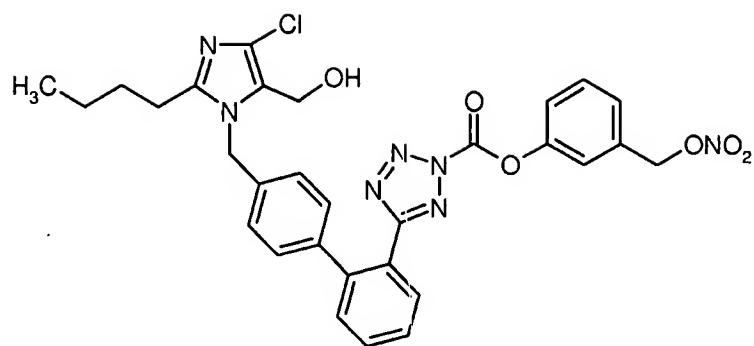
(23)



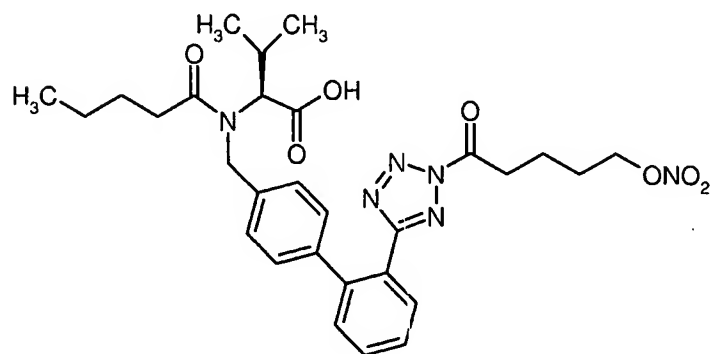
(24)



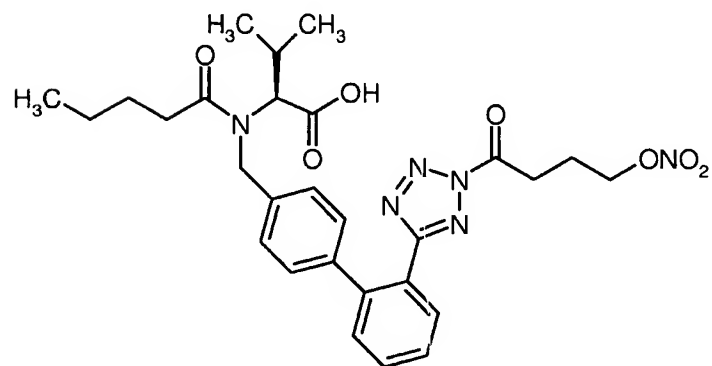
(25)



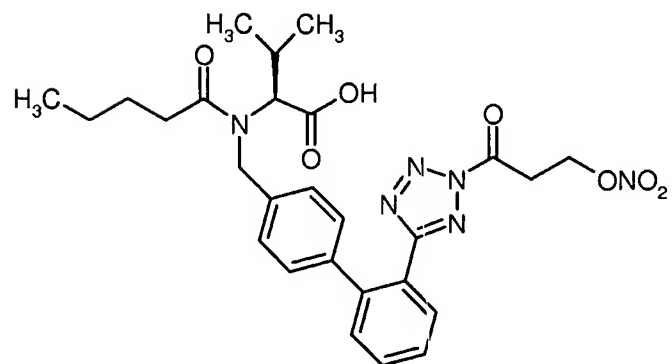
(26)



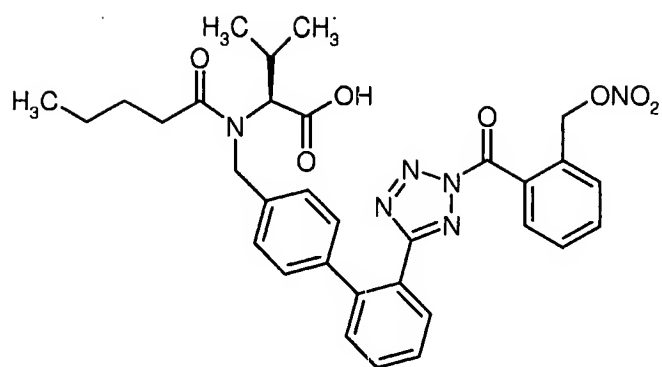
(27)



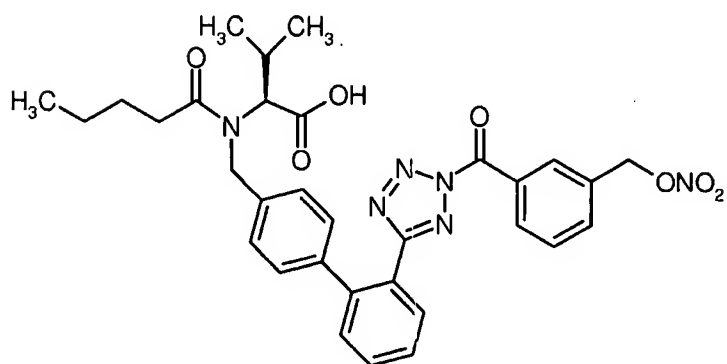
(28)



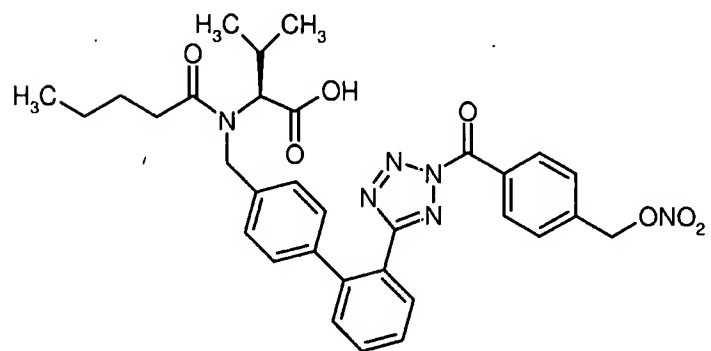
(29)



(30)

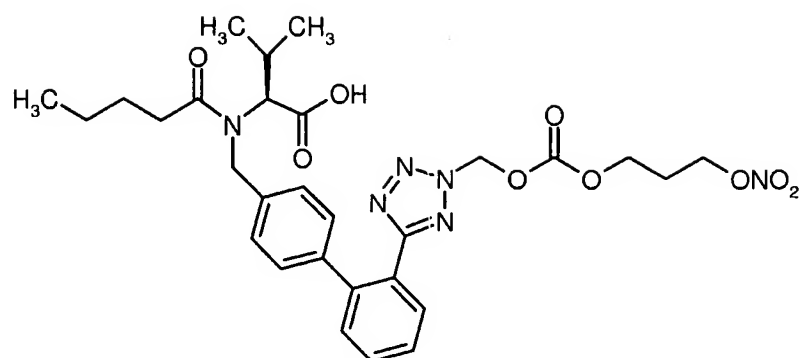


(31)

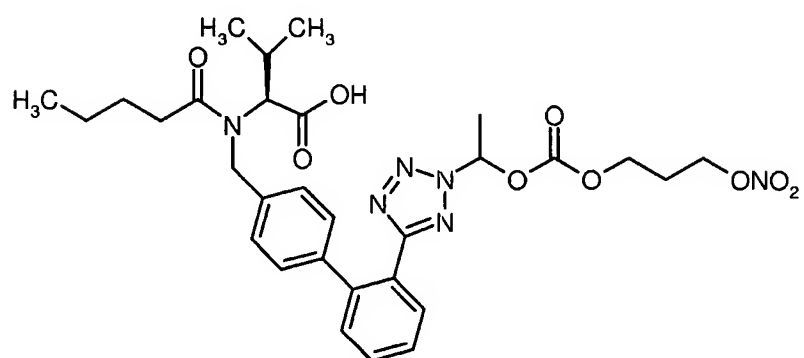


(32)

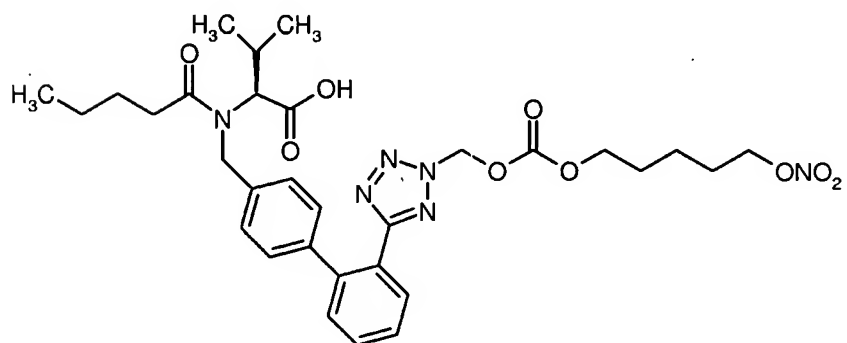
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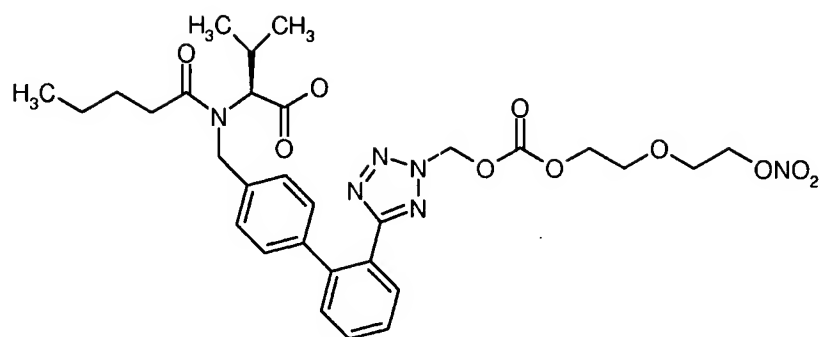
(33)



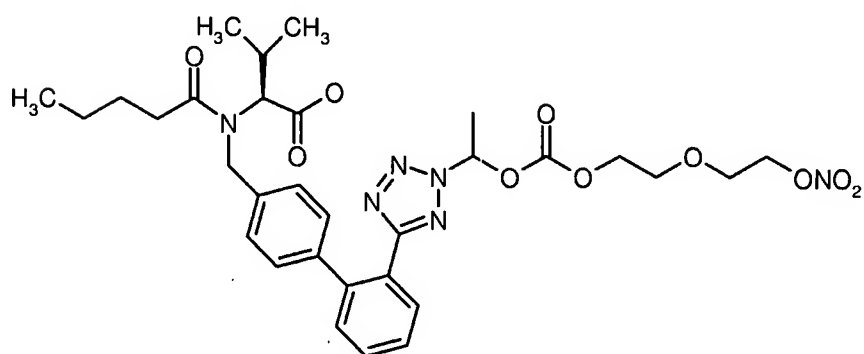
(34)



(35)

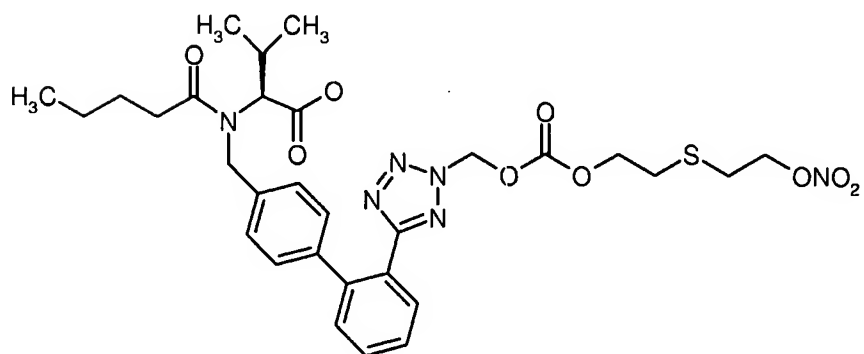


(39)

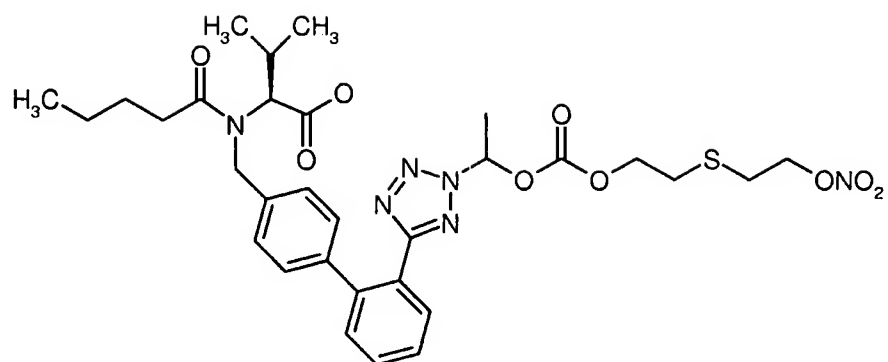


(40)

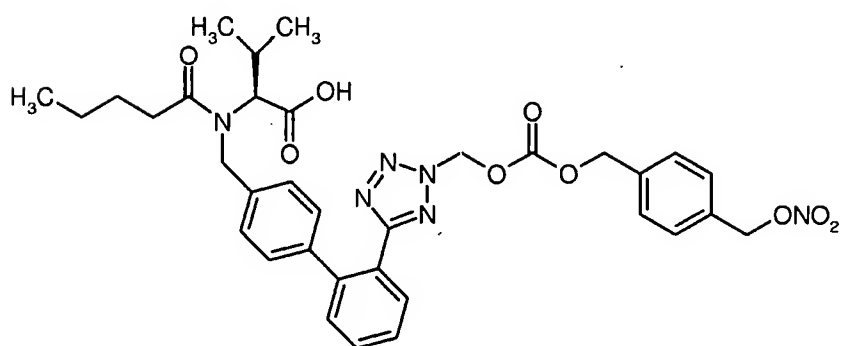
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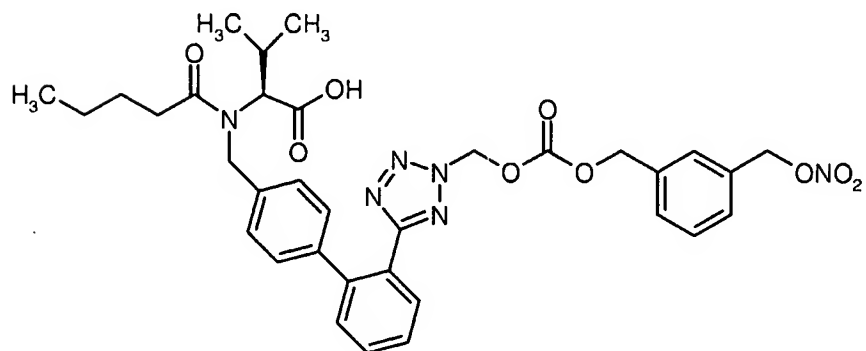
(41)



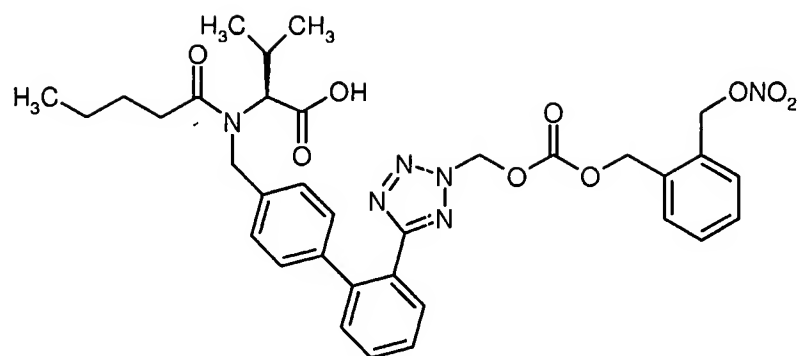
(42)



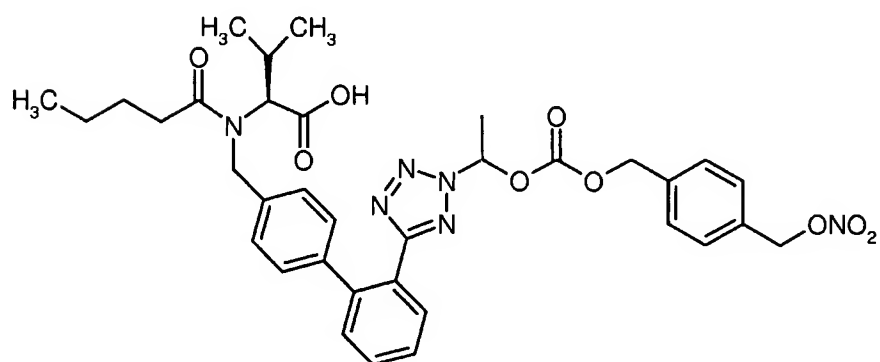
(43)



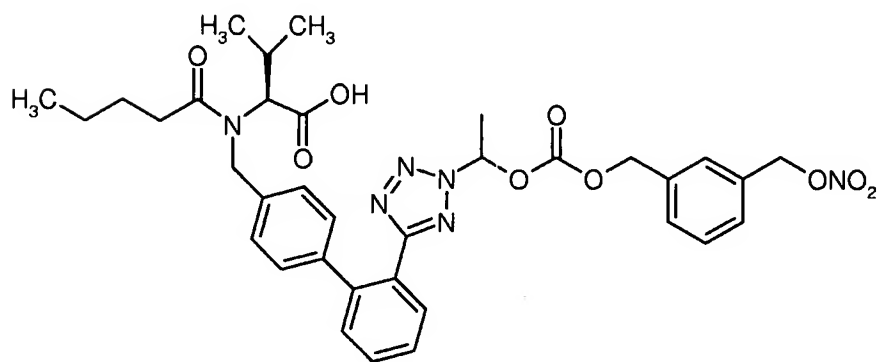
(44)



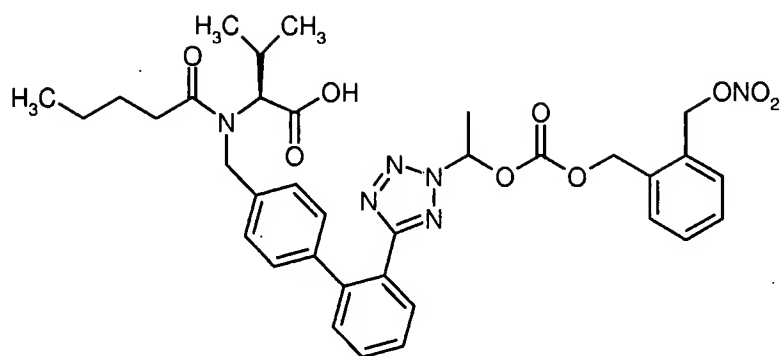
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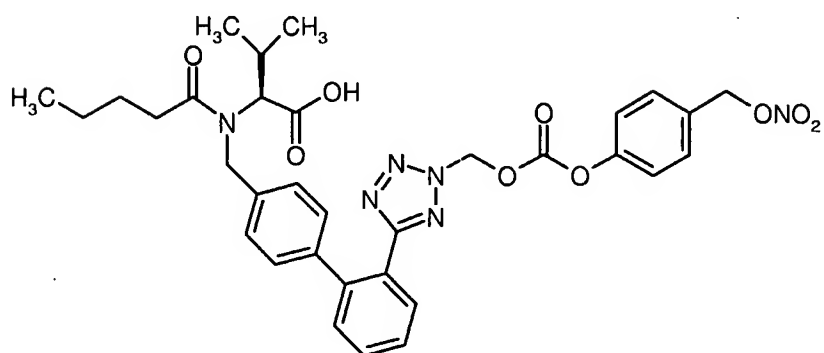
(46)



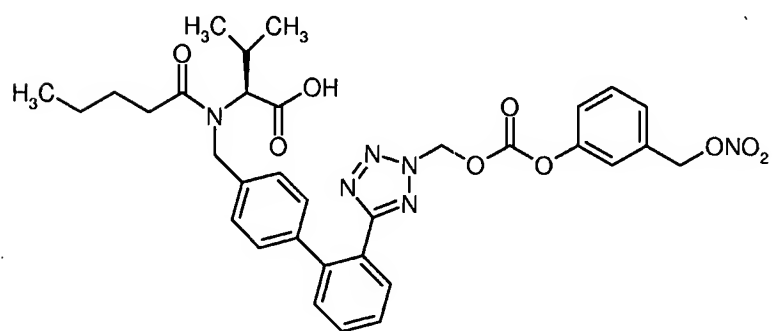
(47)



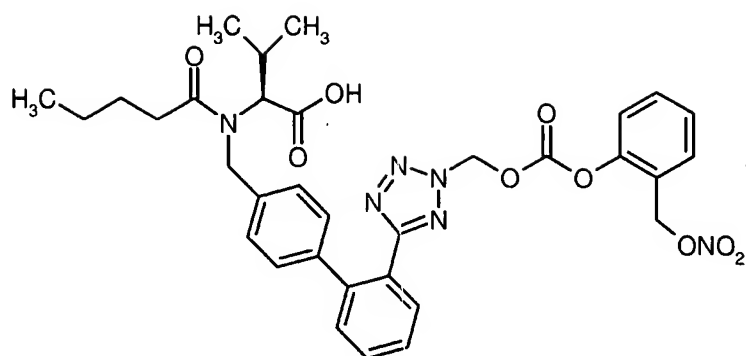
(48)



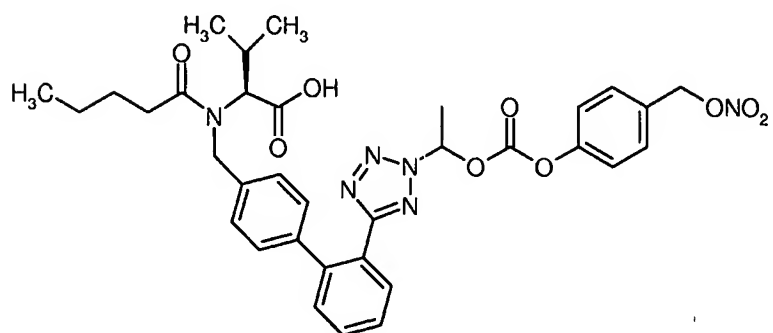
(49)



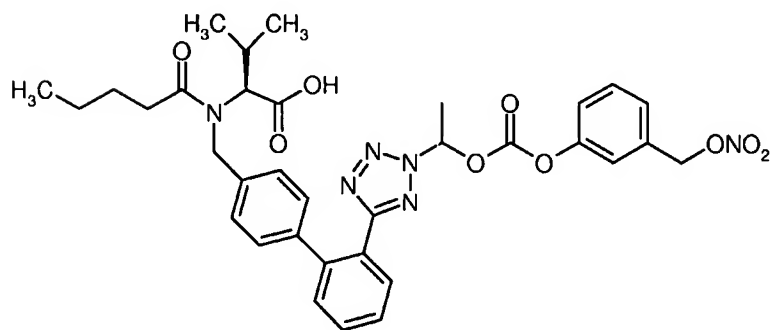
(50)



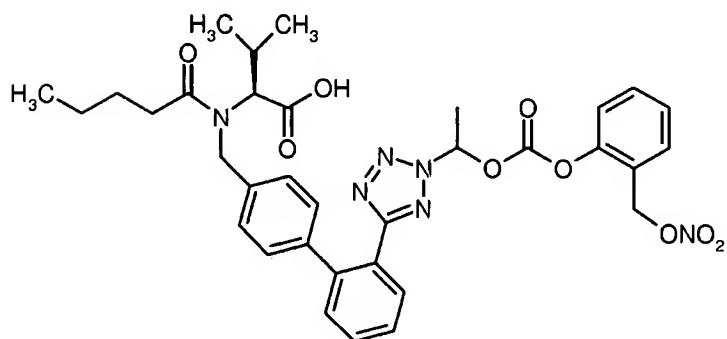
(51)



(52)

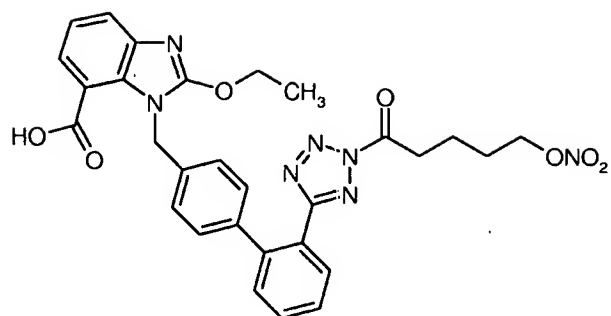


(53)

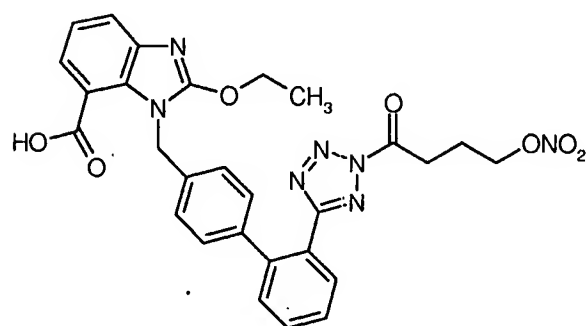


34

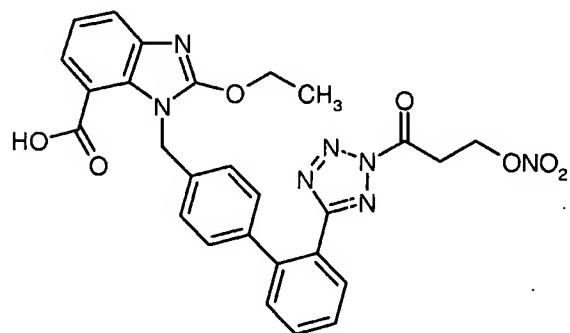
(54)



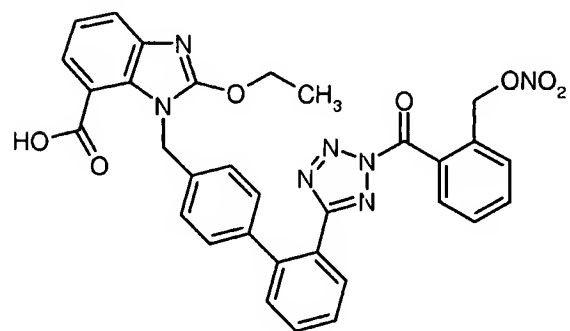
(55)



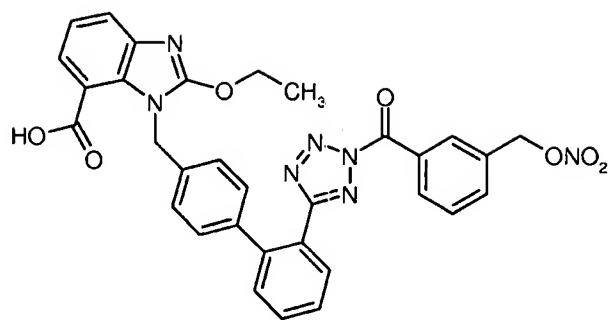
(56)



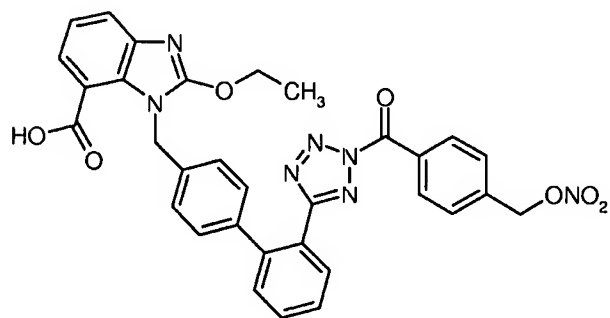
(57)



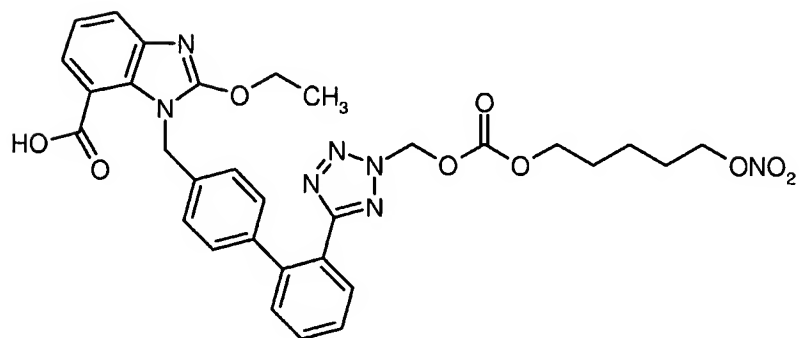
(58)



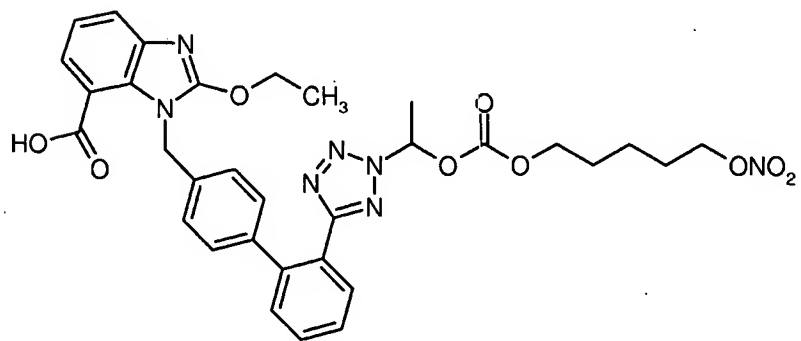
(59)



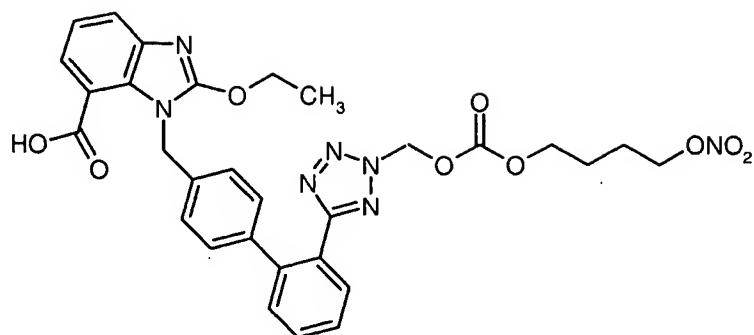
(60)



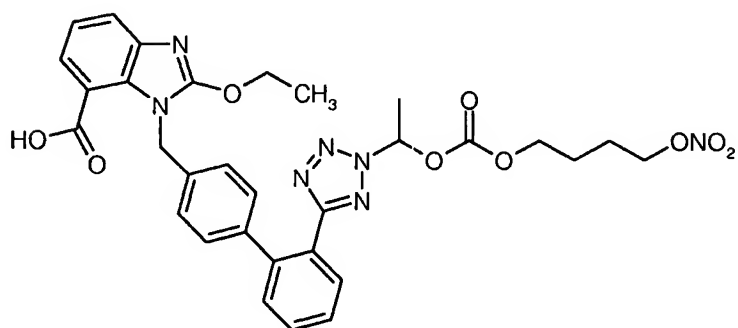
(61)



(62)

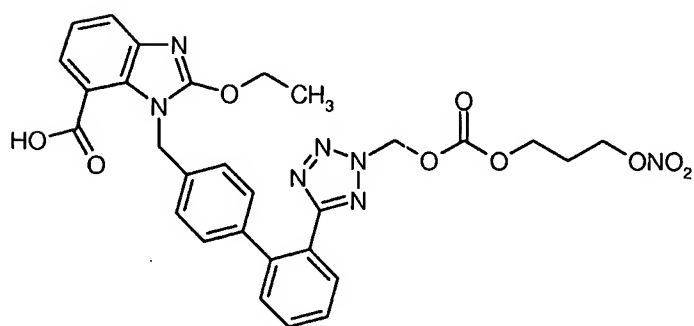


(63)

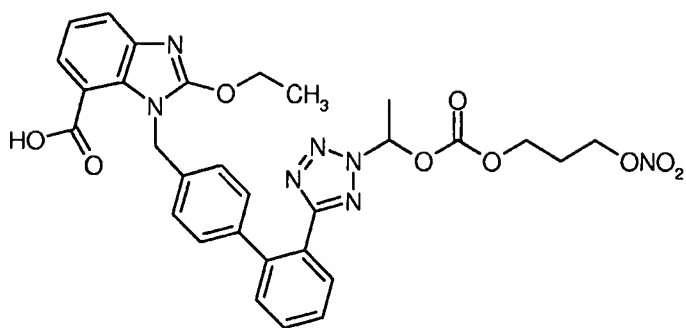


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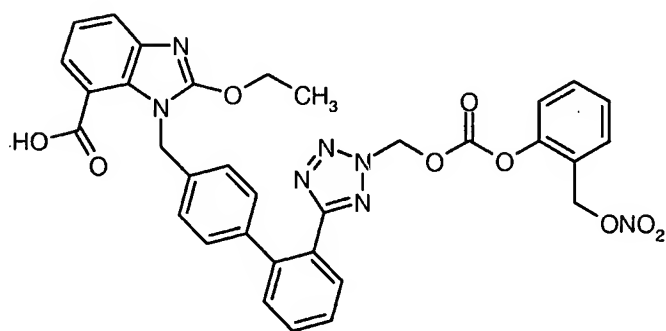
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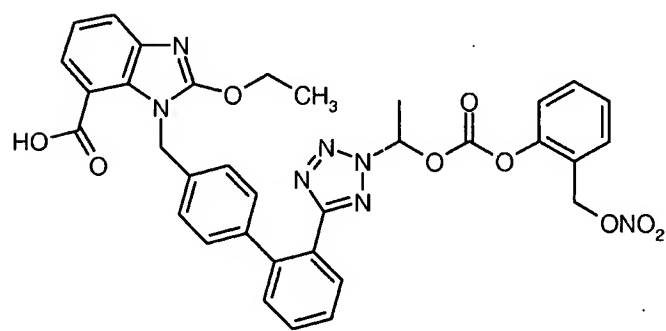
(65)



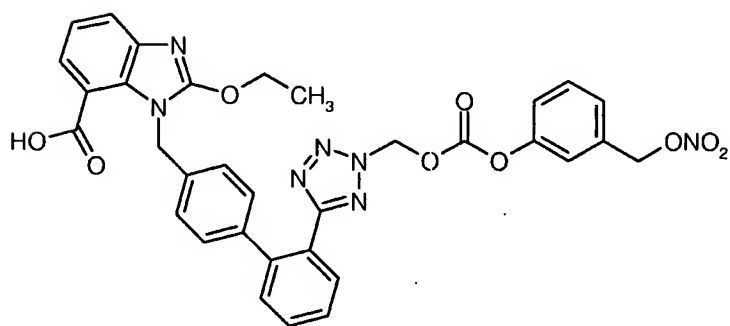
(66)



(67)

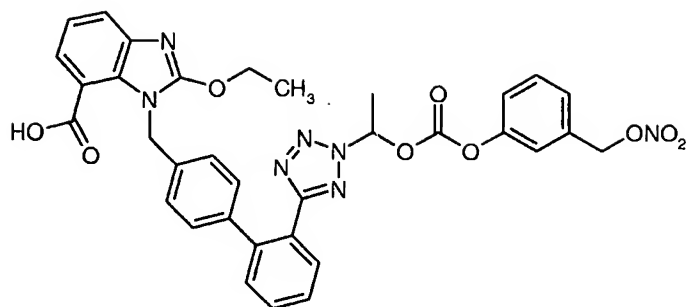


(68)

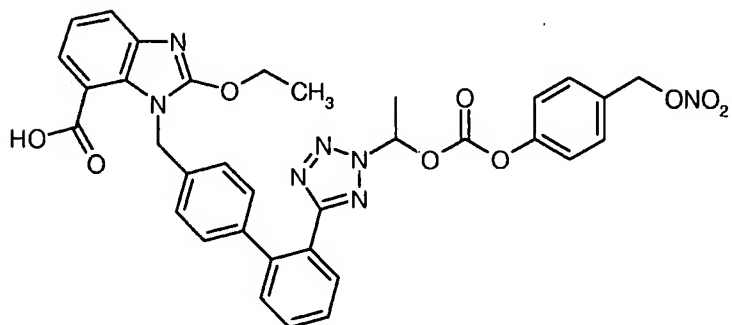


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(69)

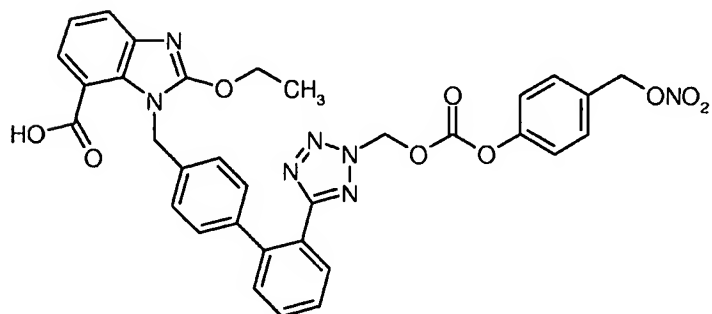


(70)

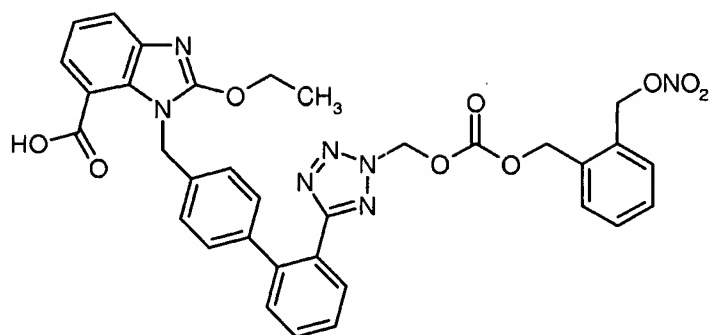


5

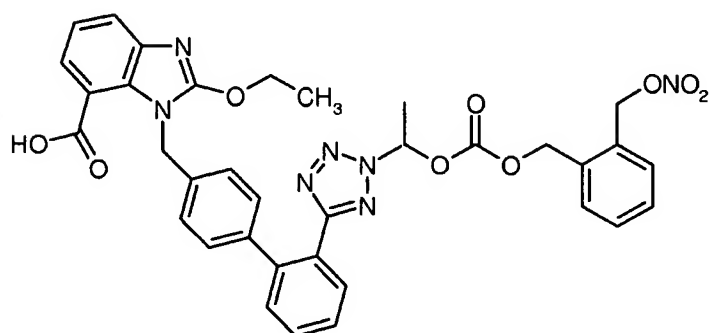
(71)



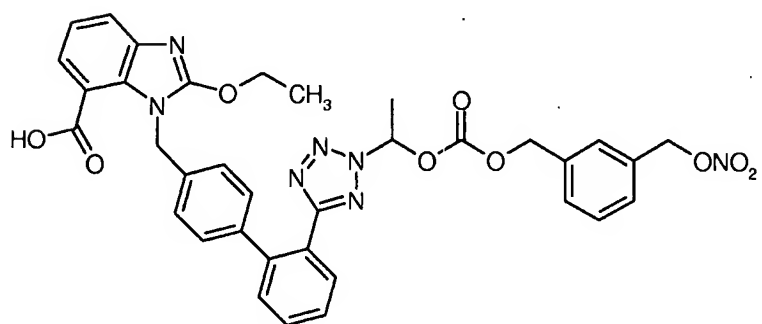
(72)



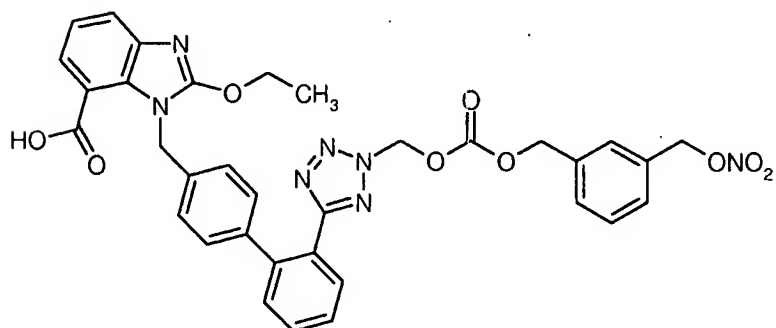
(73)



(74)

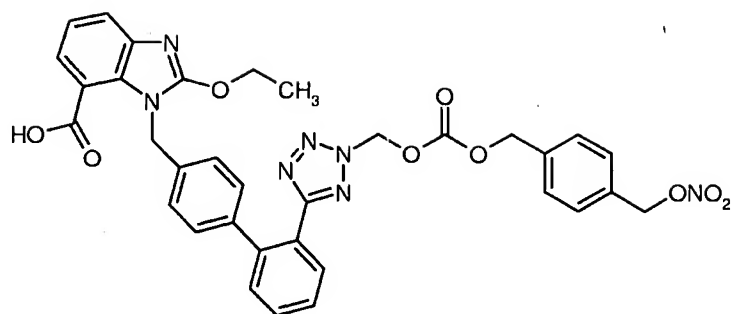


(75)

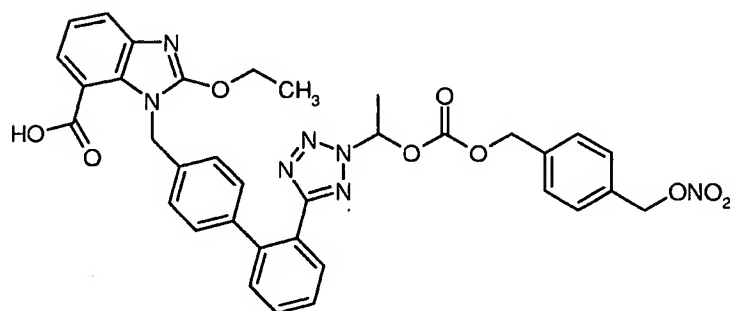


40

(76)

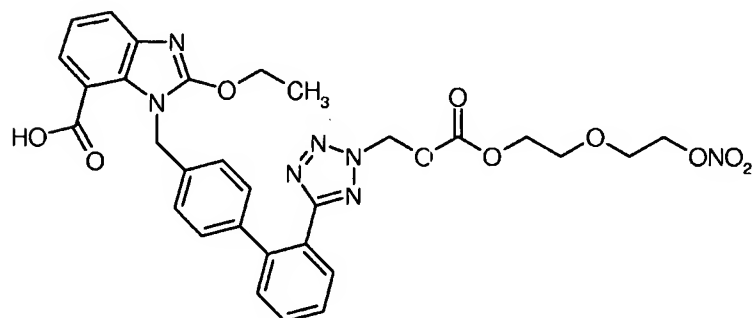


(77)

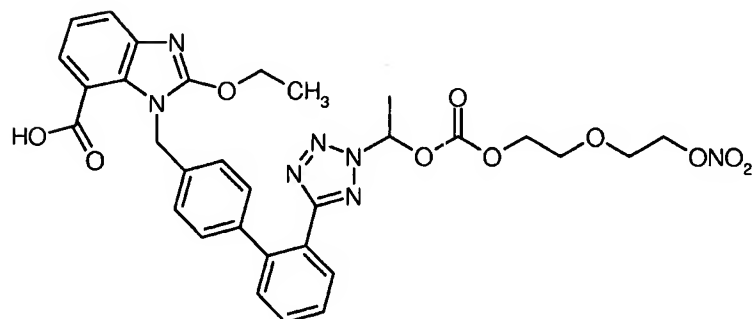


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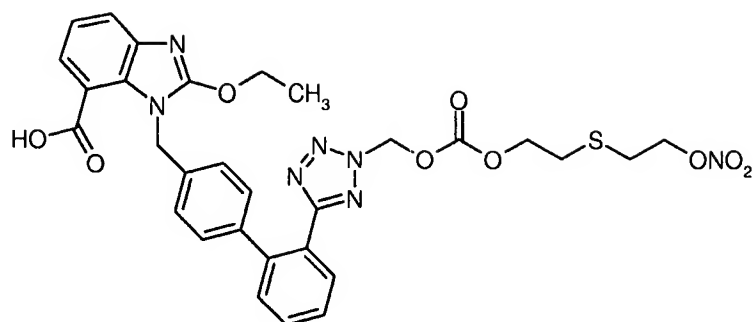
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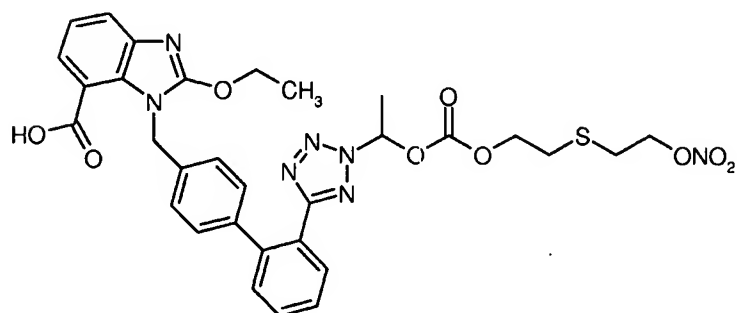
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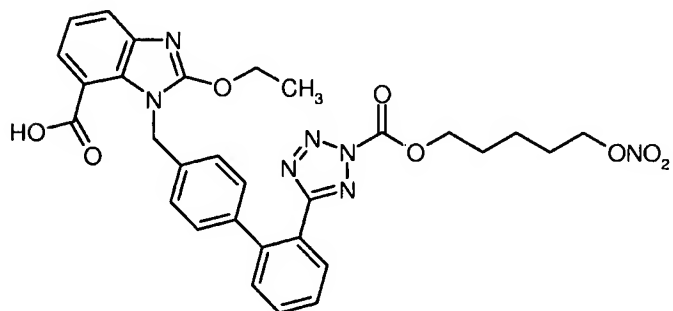
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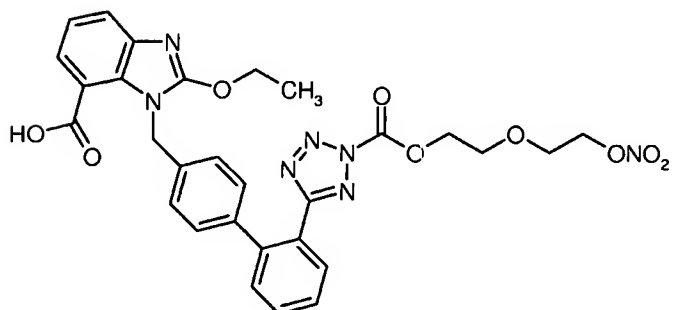
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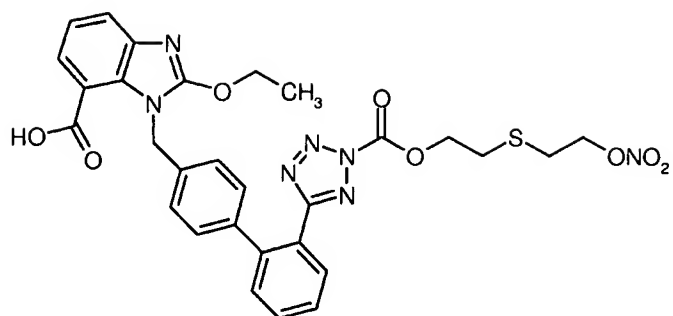
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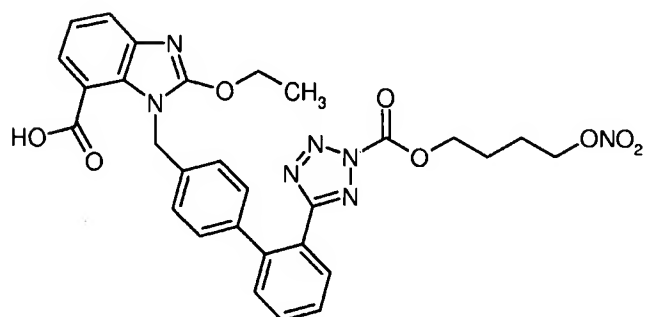
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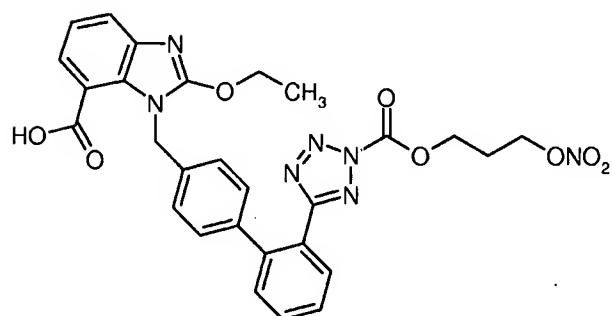
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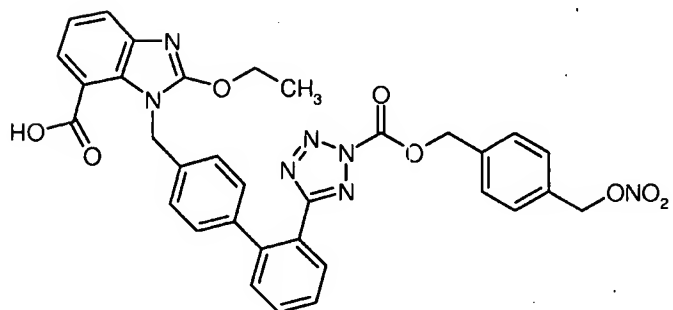
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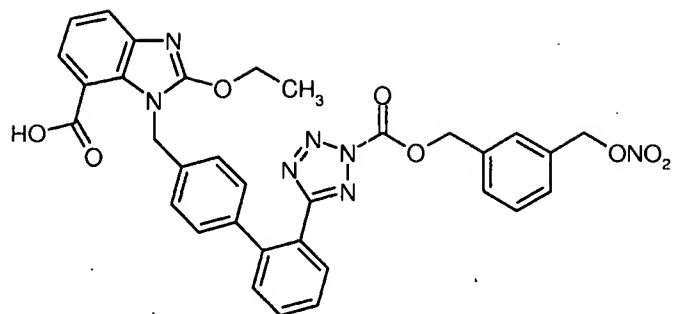
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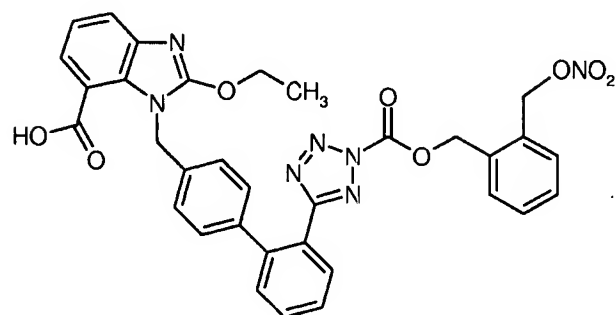
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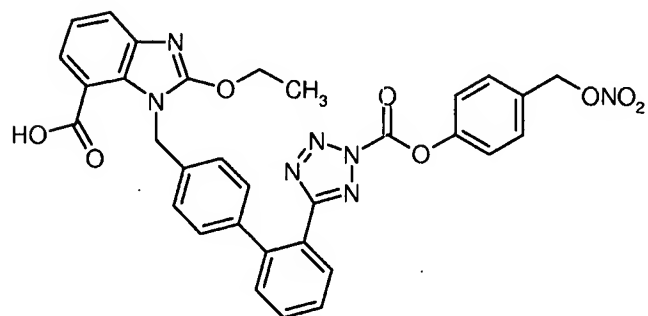
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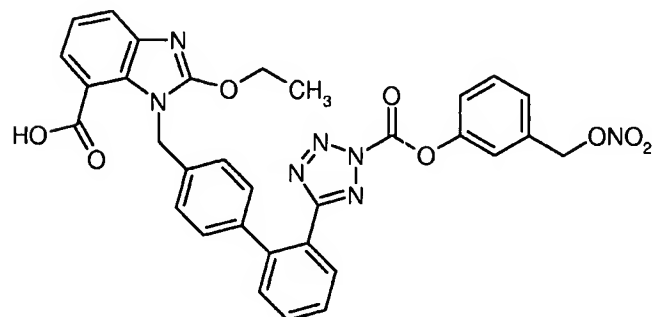
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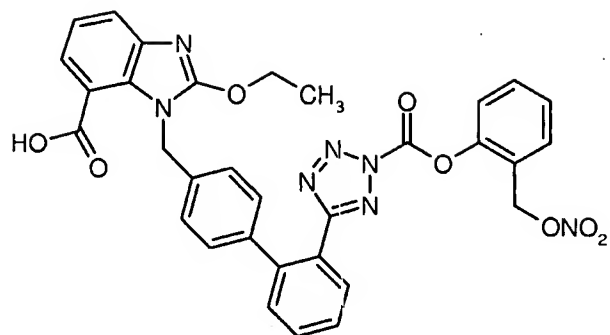
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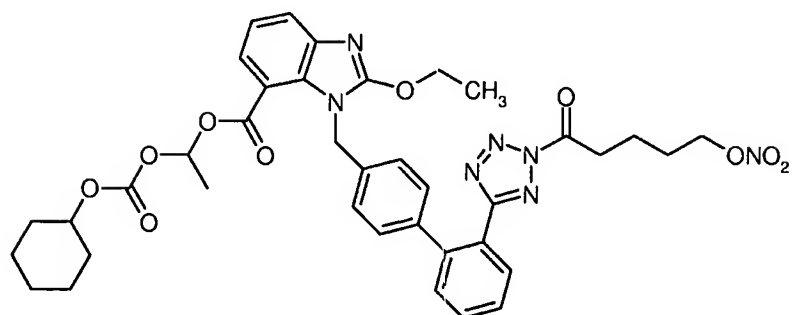
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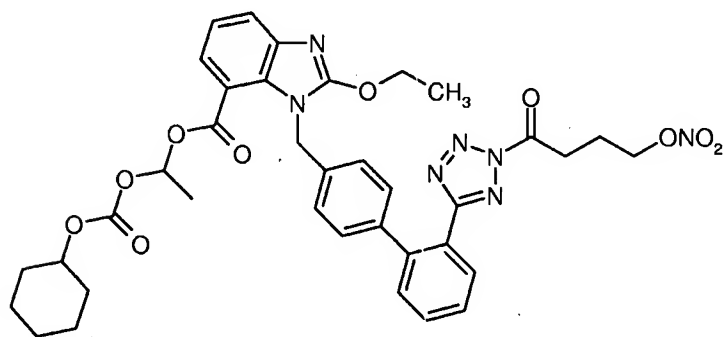
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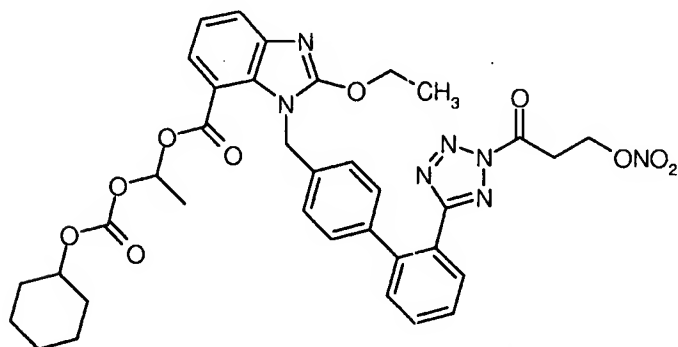
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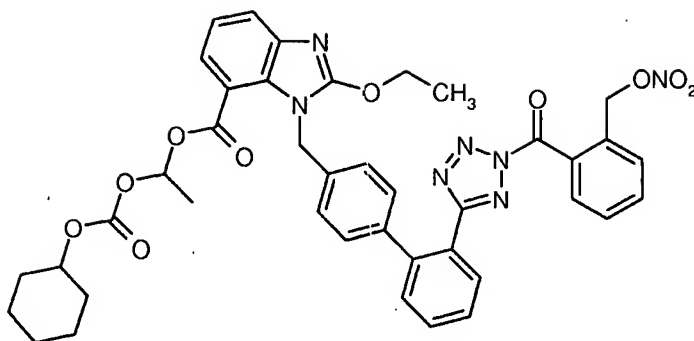
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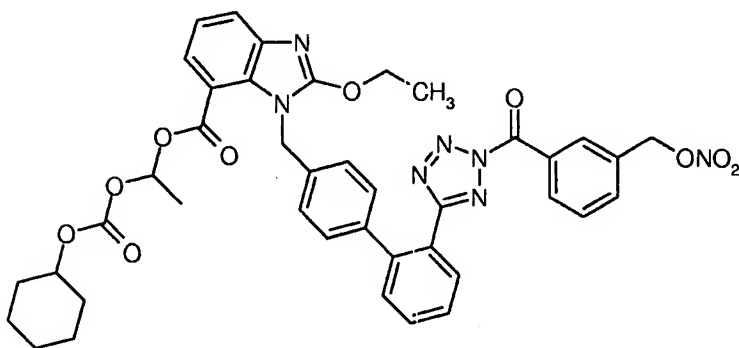
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(96)

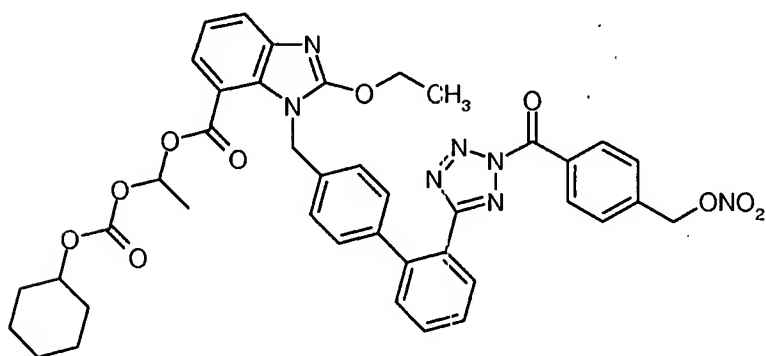


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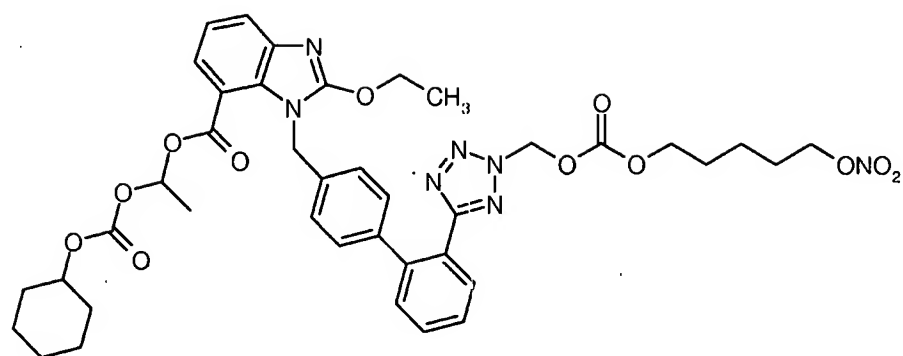


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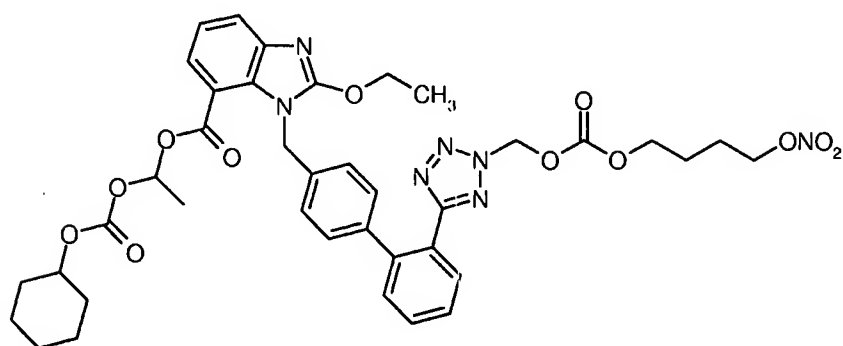
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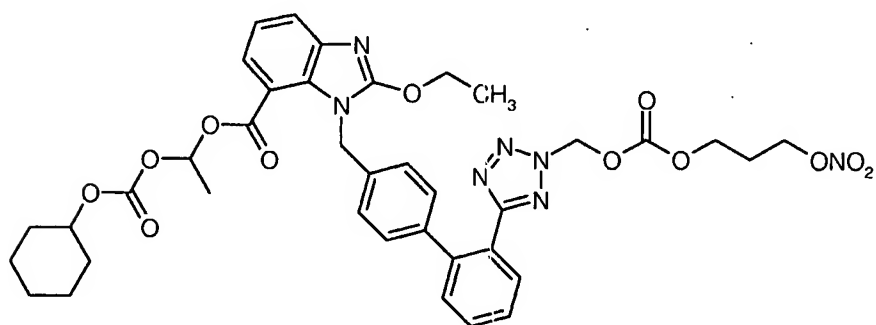
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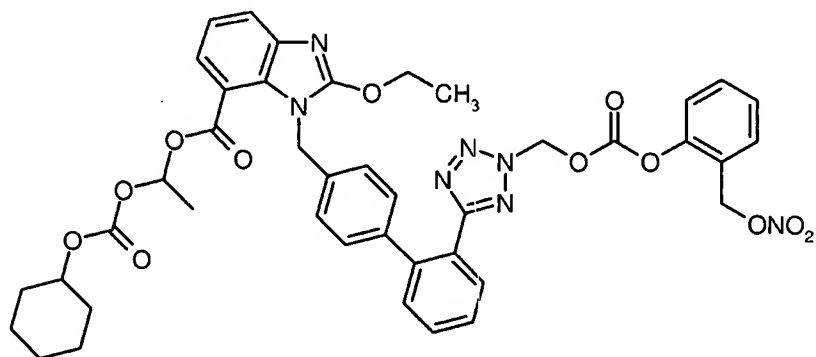
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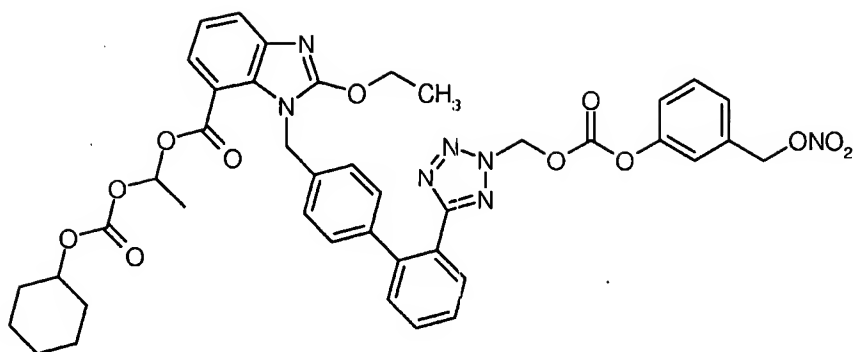
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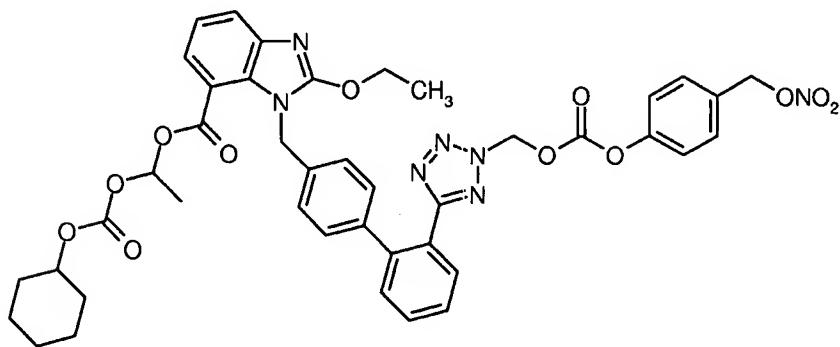
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(103)

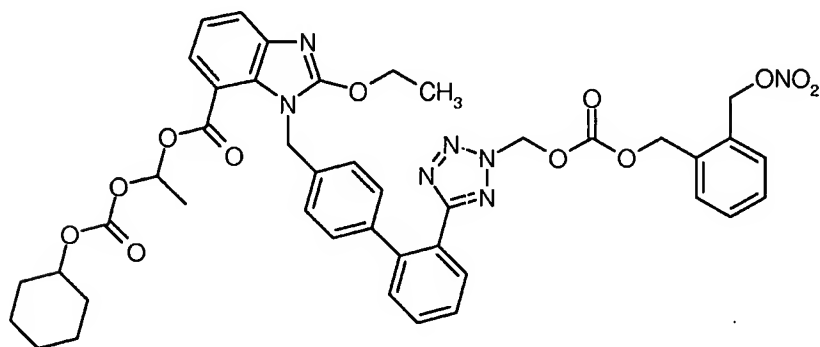


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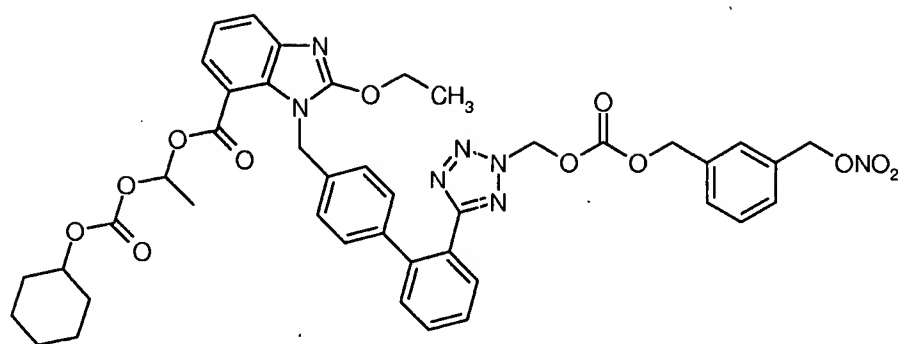


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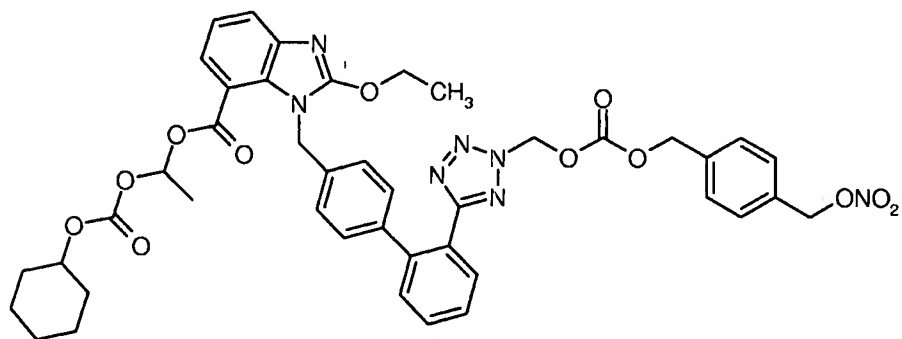
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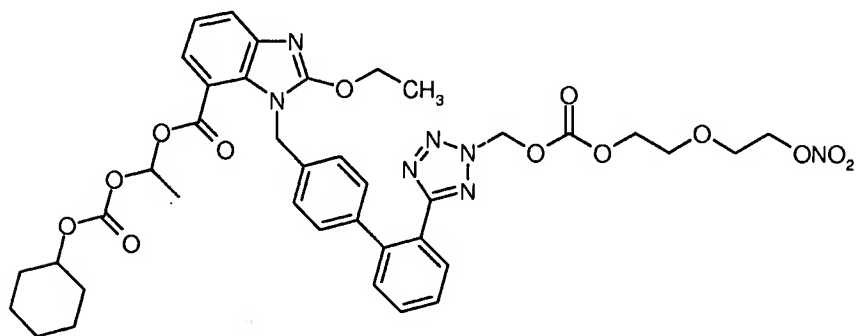
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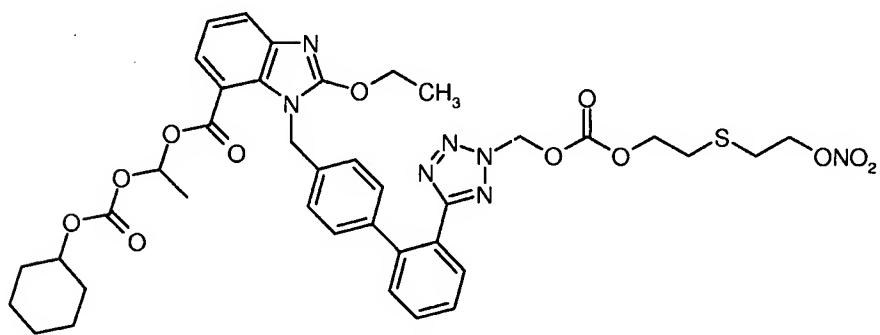
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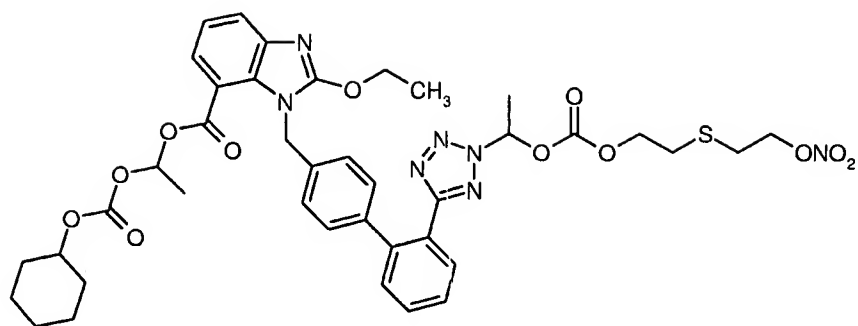
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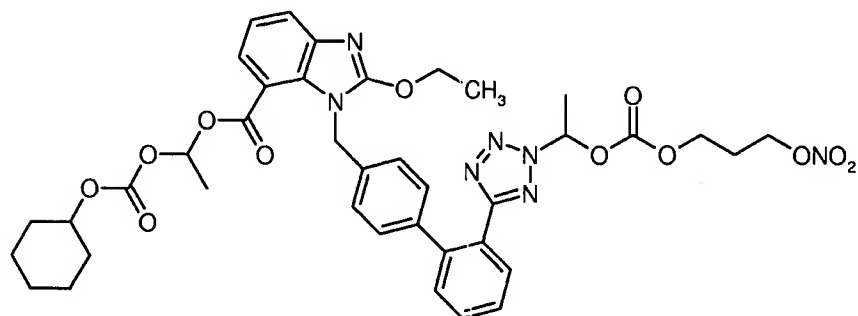
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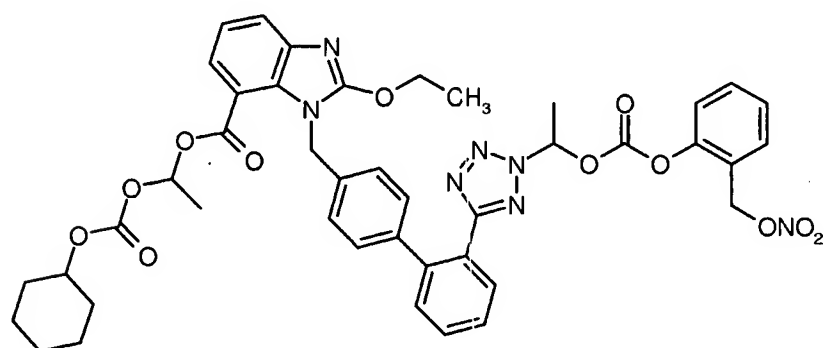
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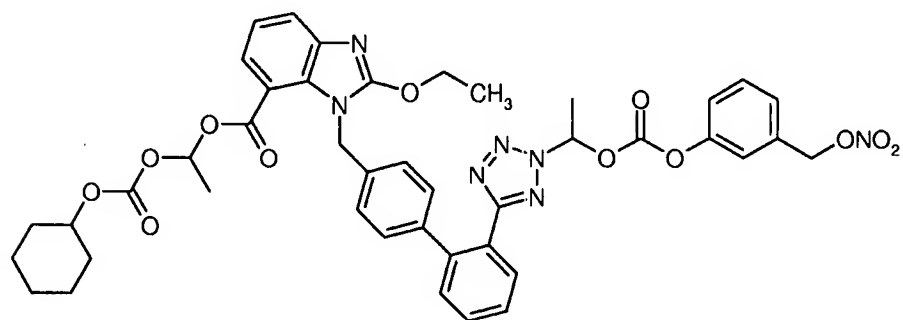
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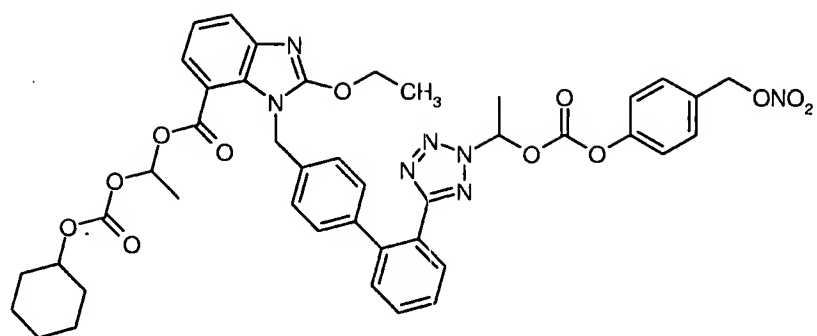
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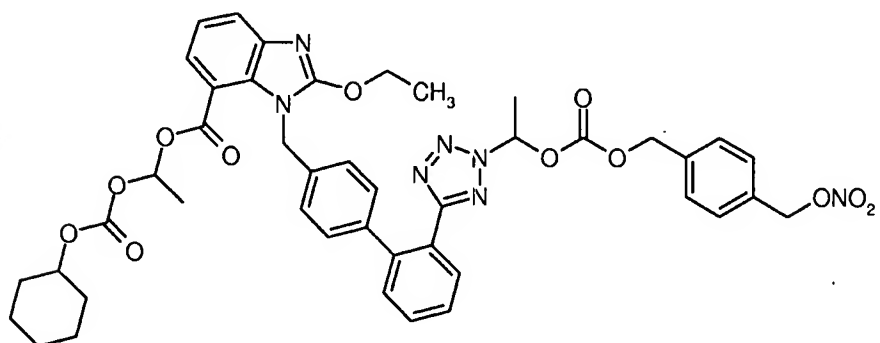
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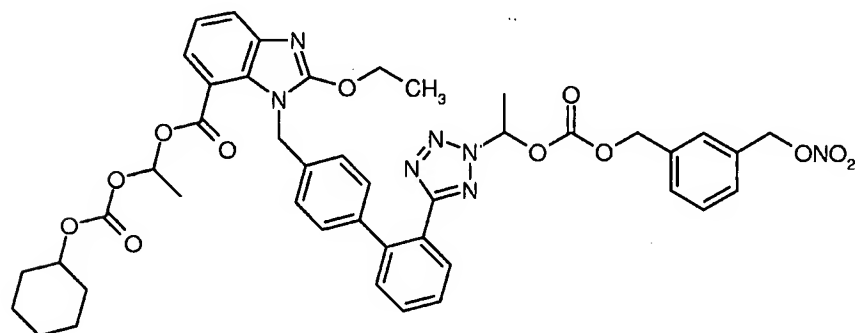
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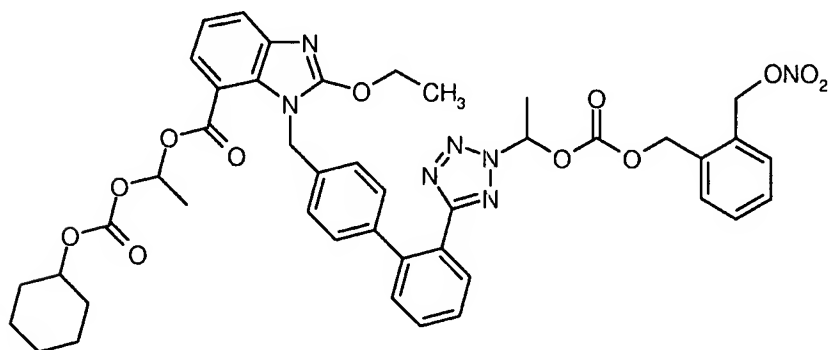
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(116)

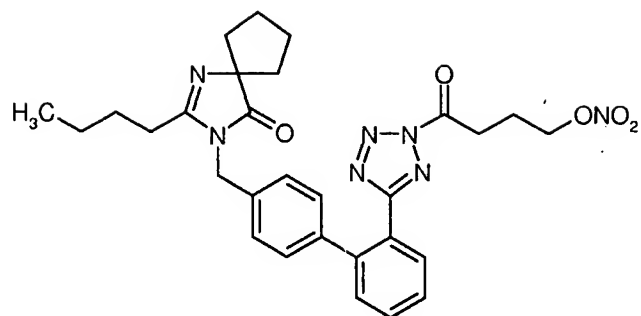


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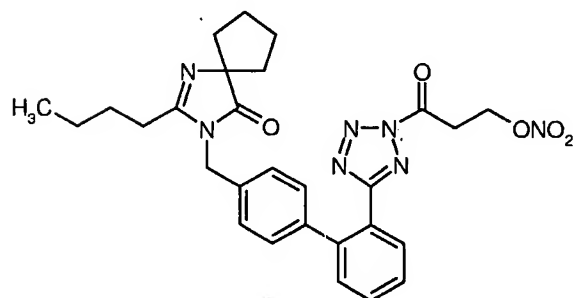


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(118)

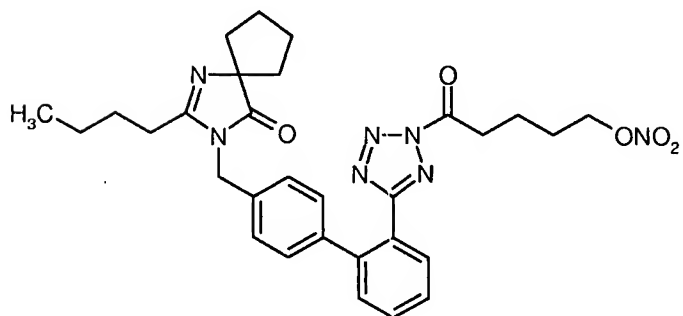


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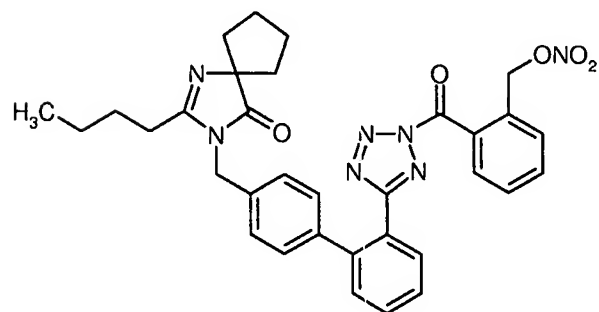


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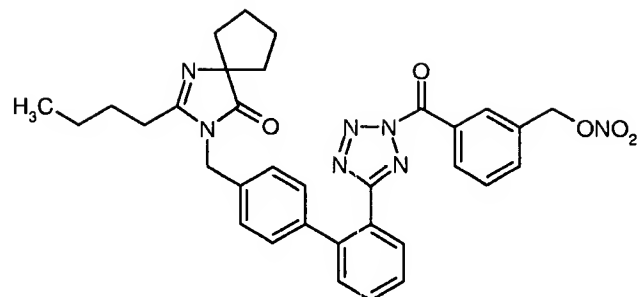
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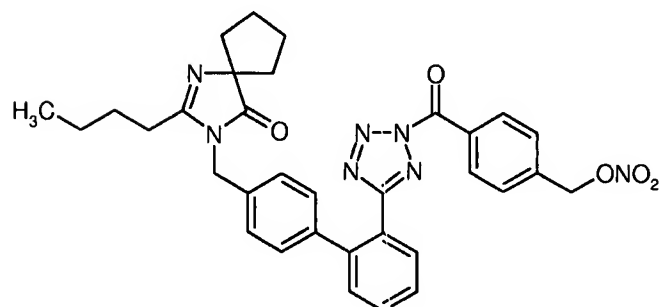
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(122)

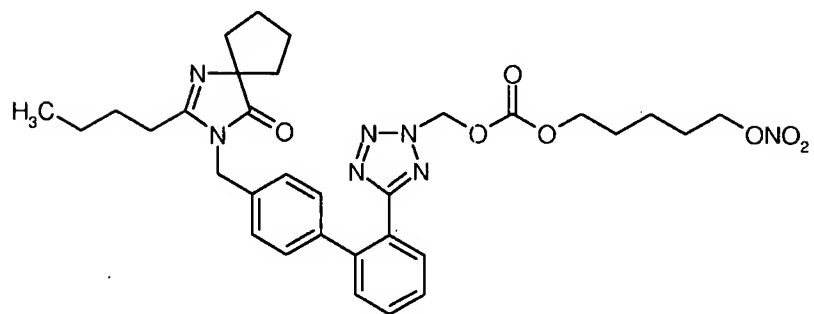


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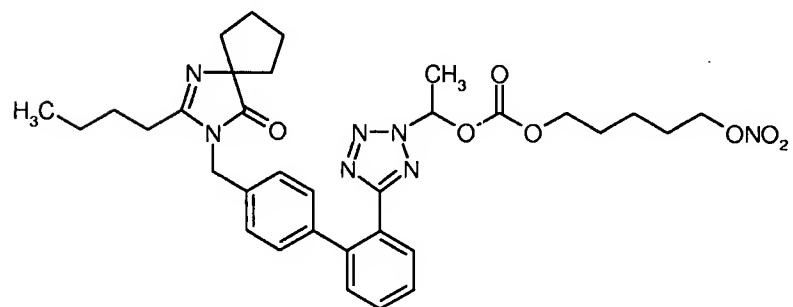


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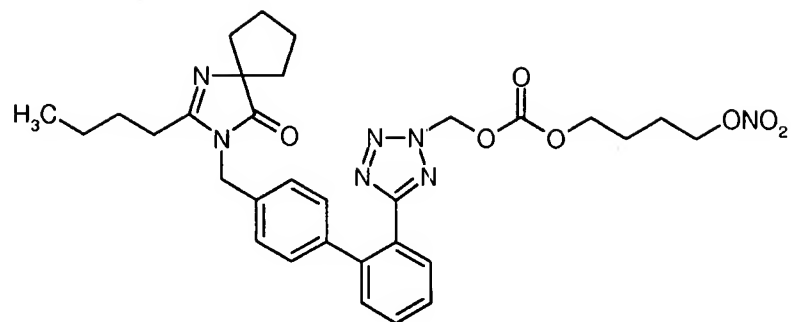
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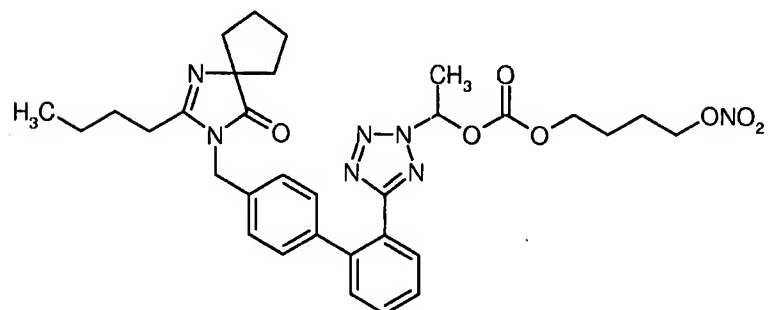
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(126)

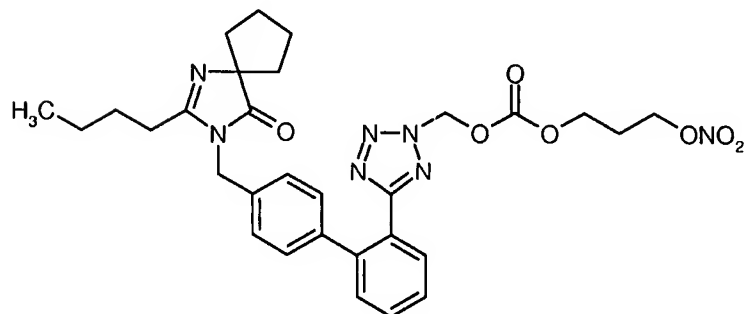


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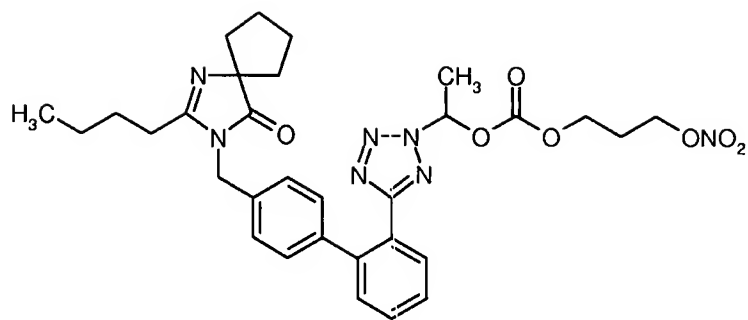


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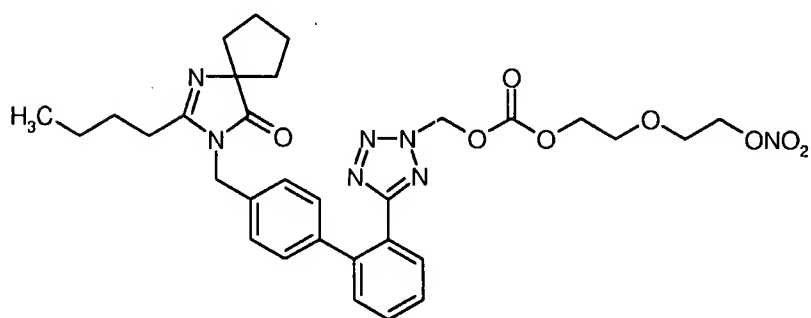
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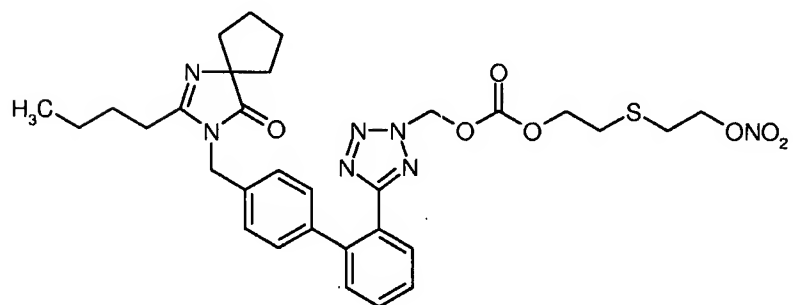
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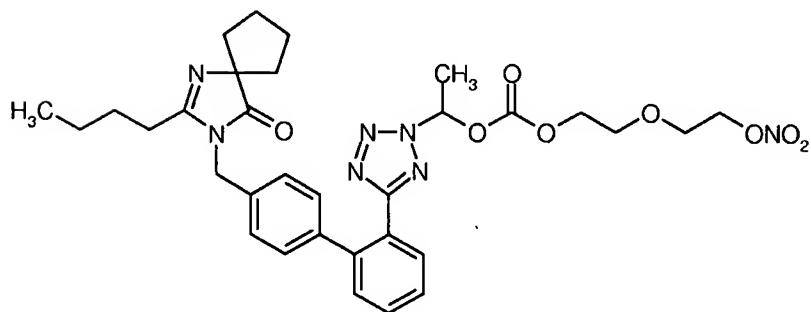
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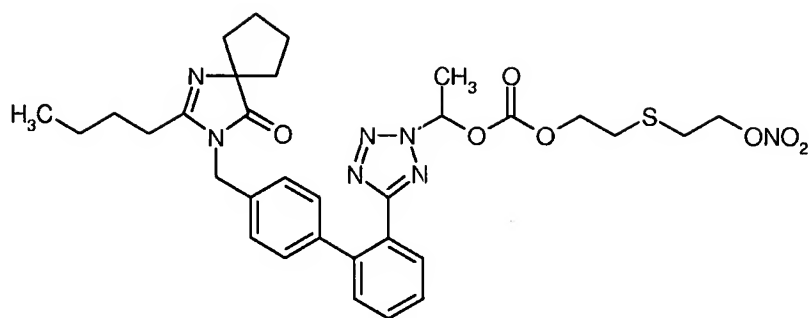
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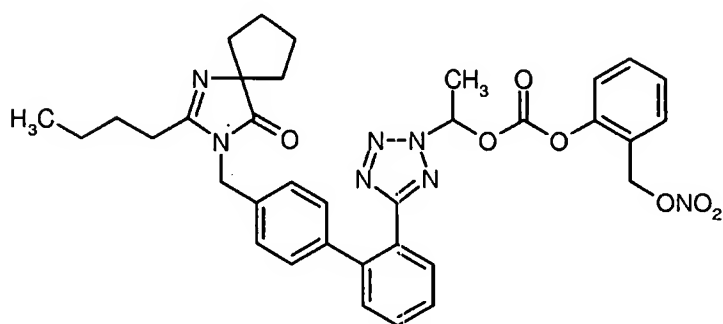
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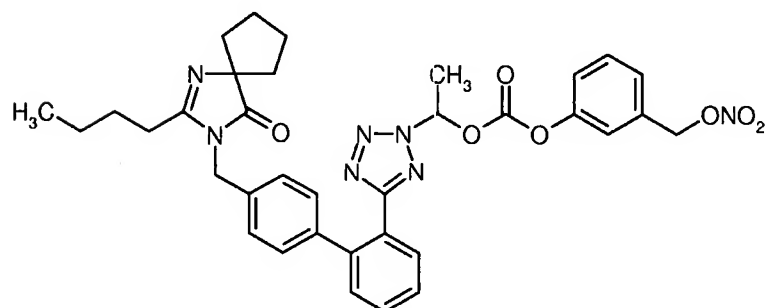
(133)



(134)

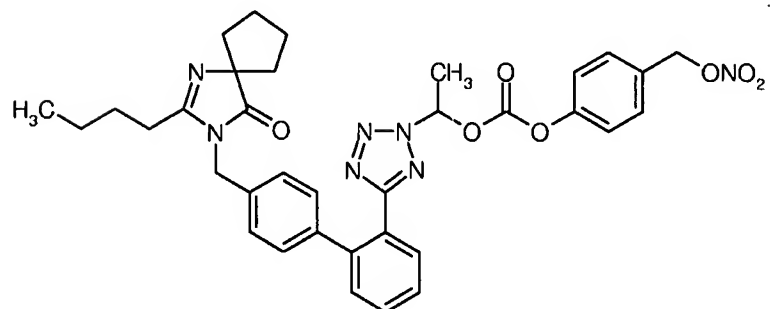


(135)

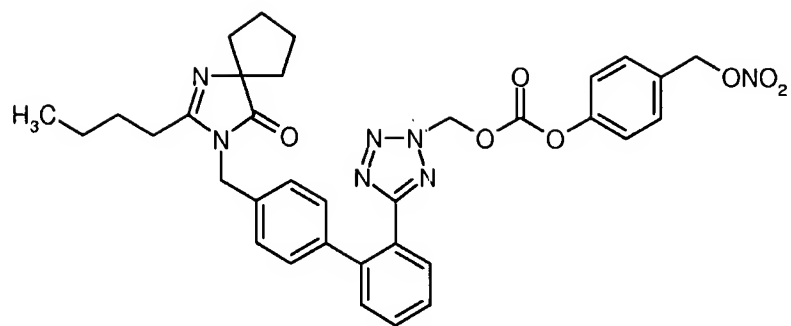


(136)

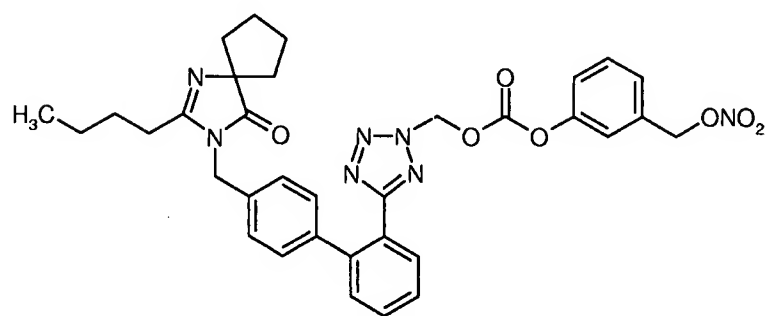
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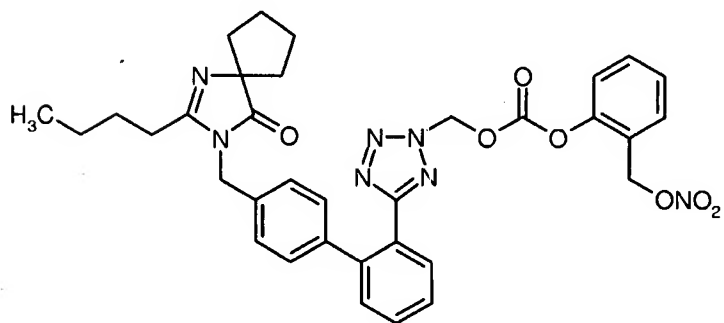
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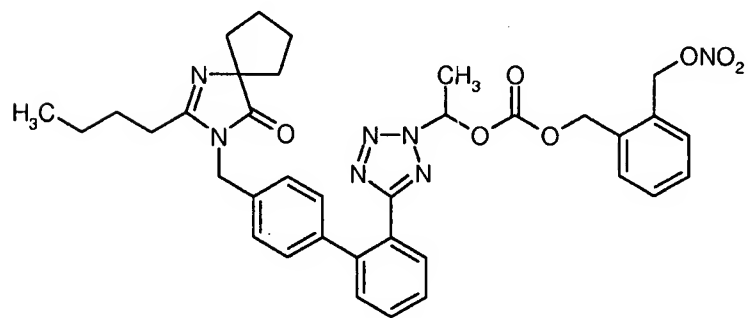
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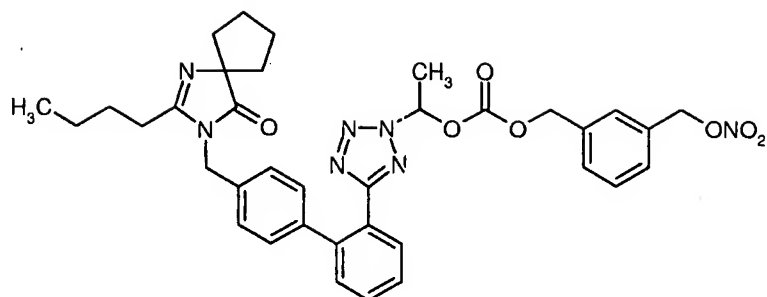
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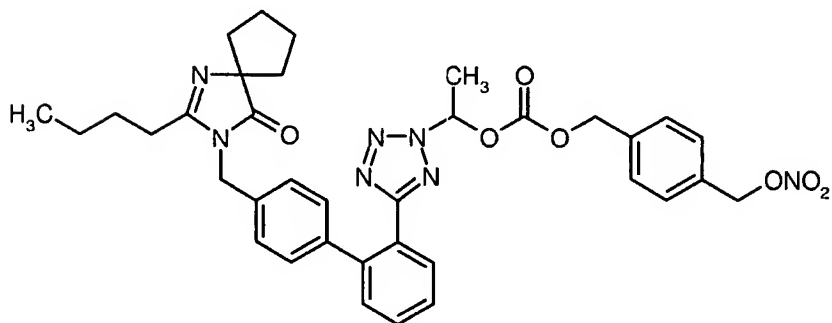
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(141)

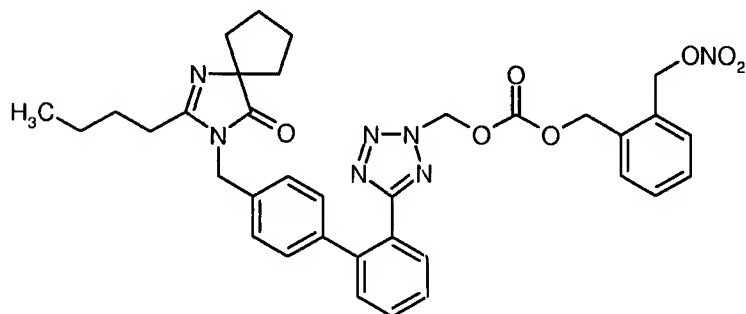


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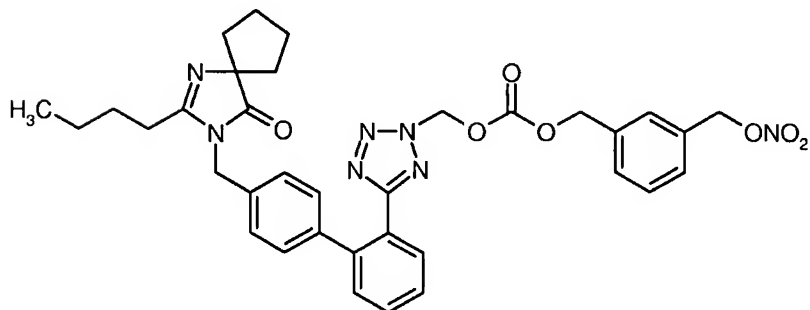


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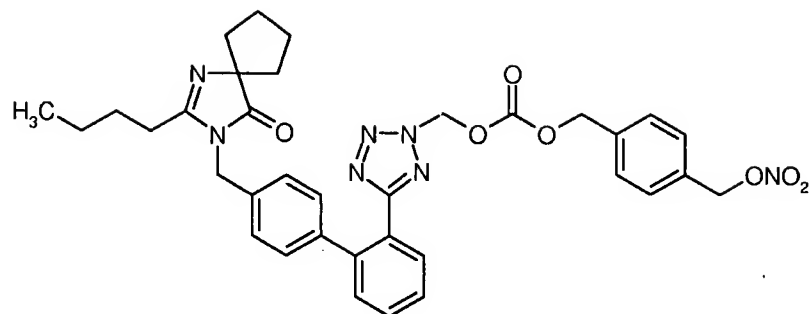
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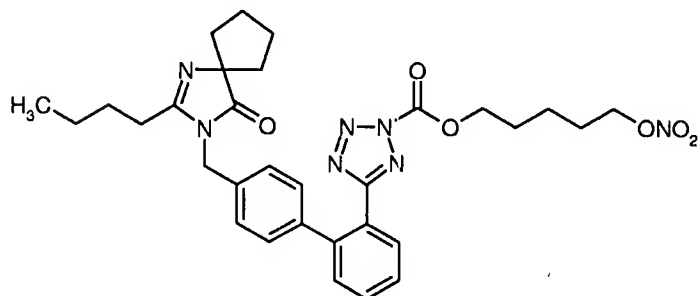
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(145)

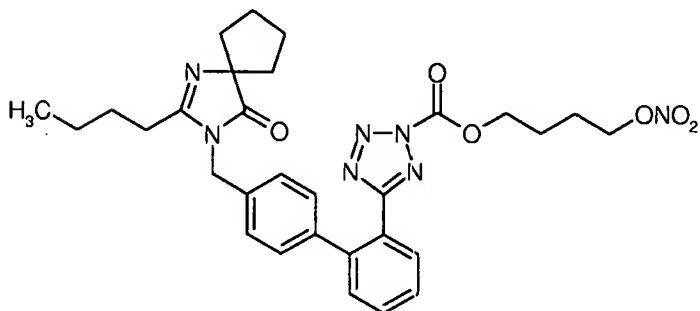


(146)

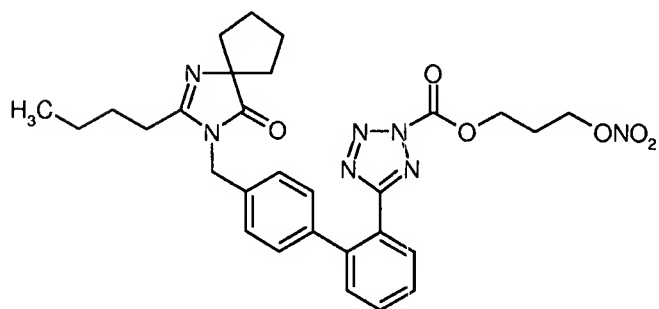


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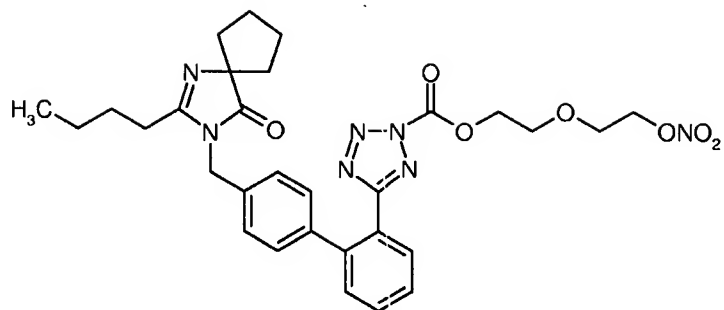
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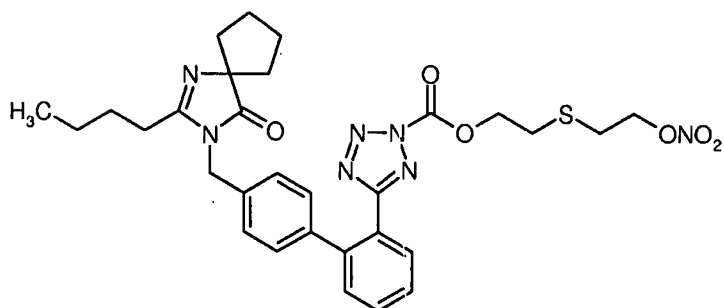
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(149)

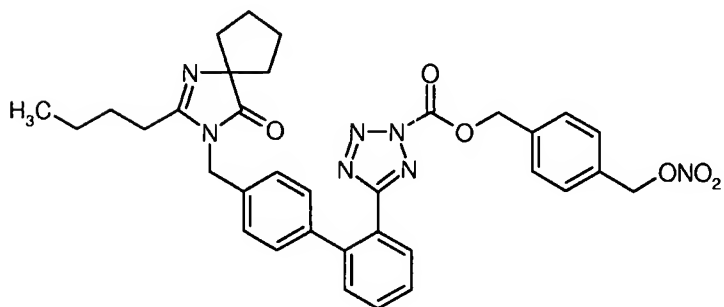


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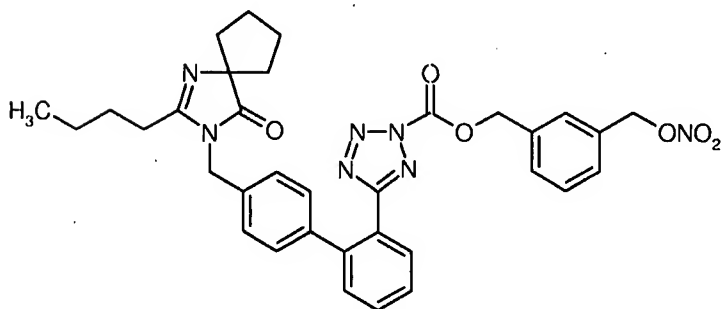


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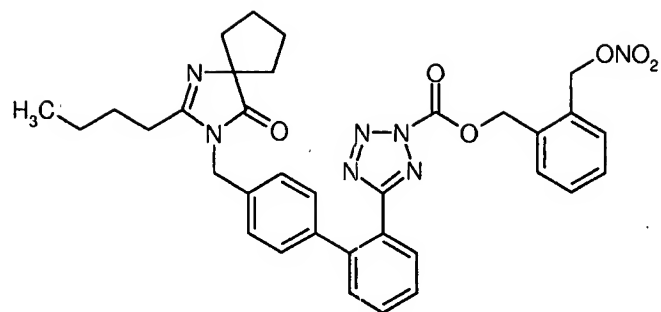
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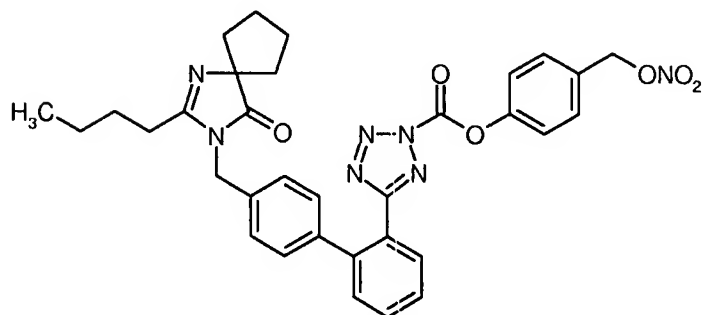
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(153)

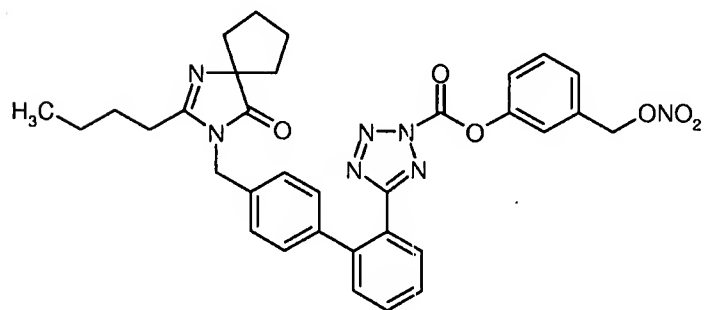


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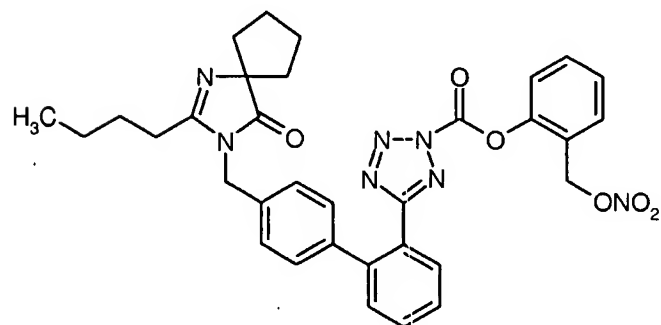


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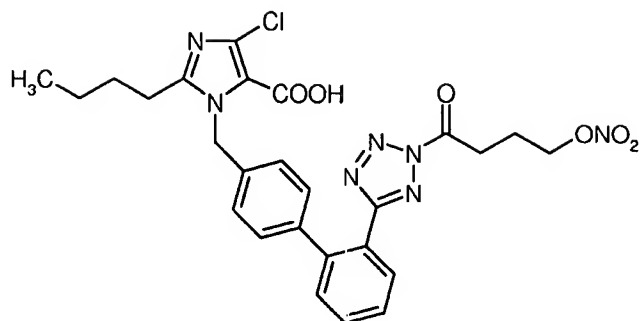
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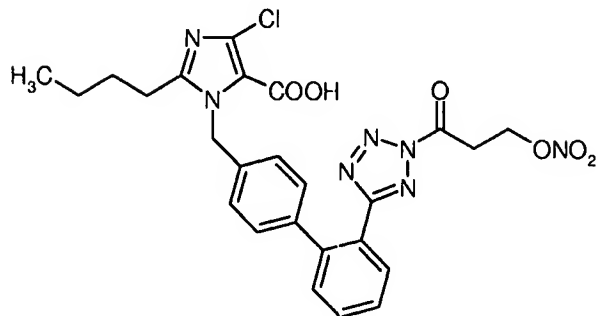
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(157)

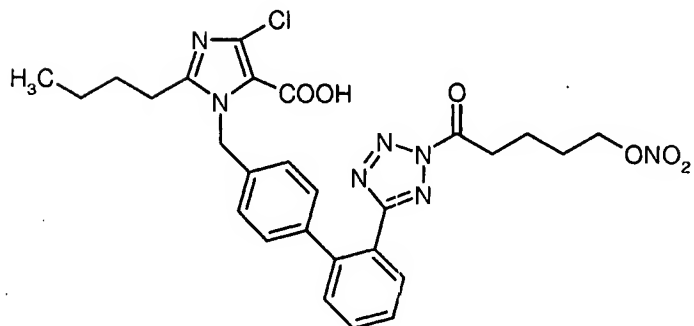


(158)

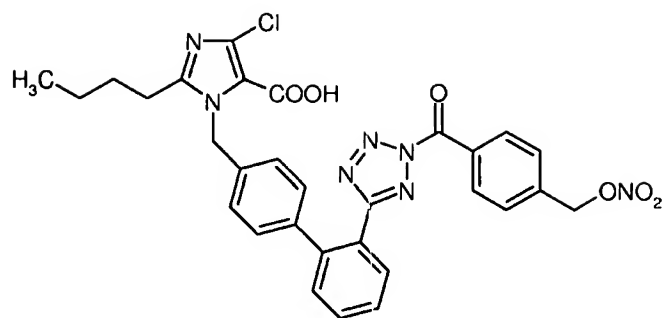


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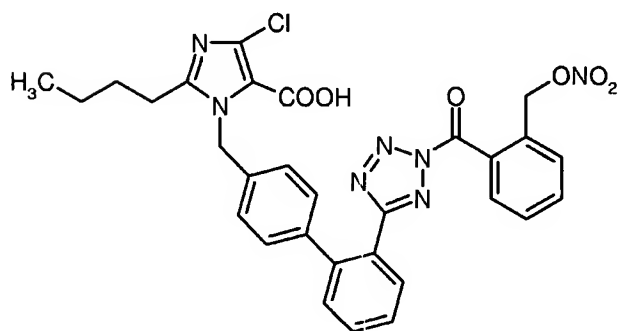
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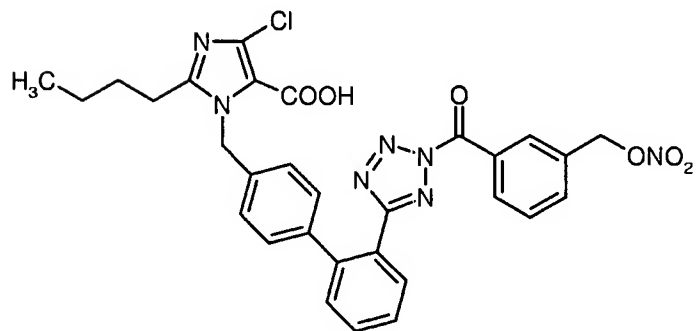
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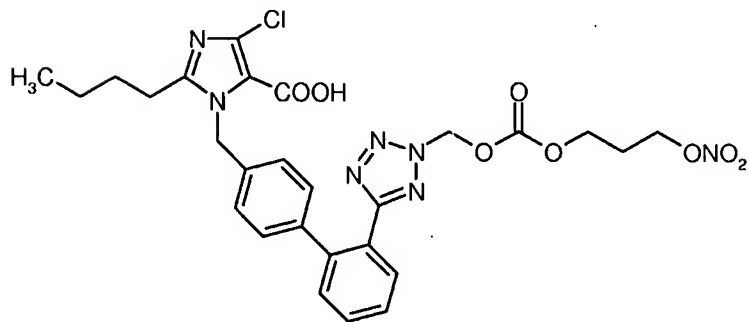
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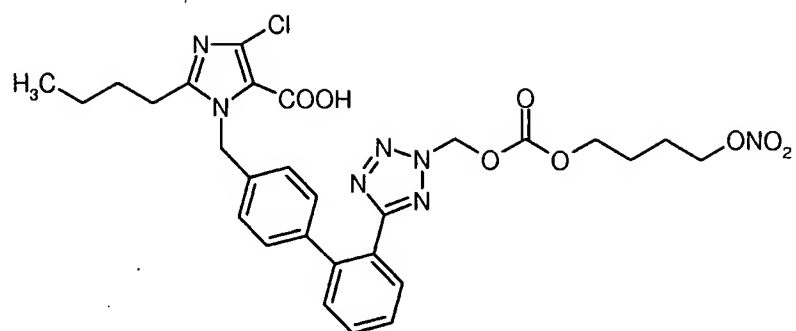
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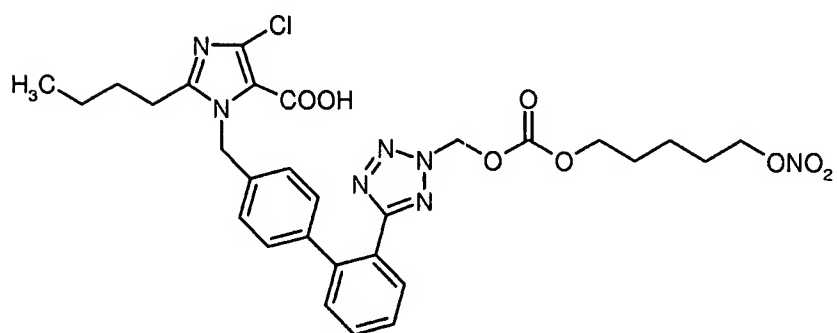
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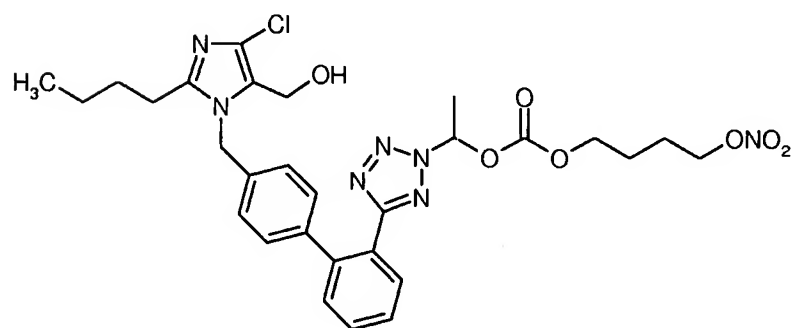
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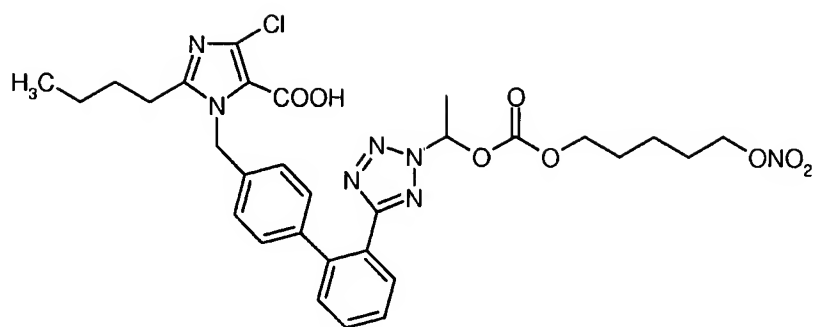
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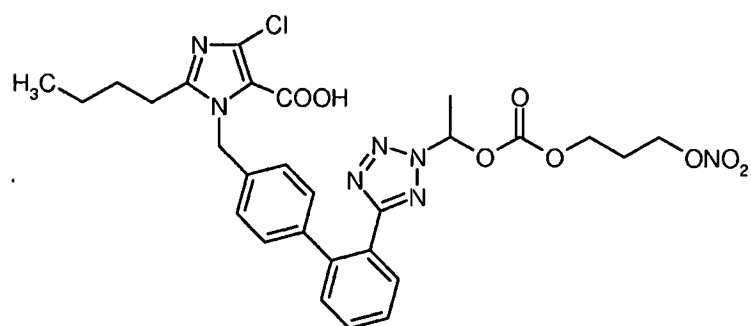
(166)



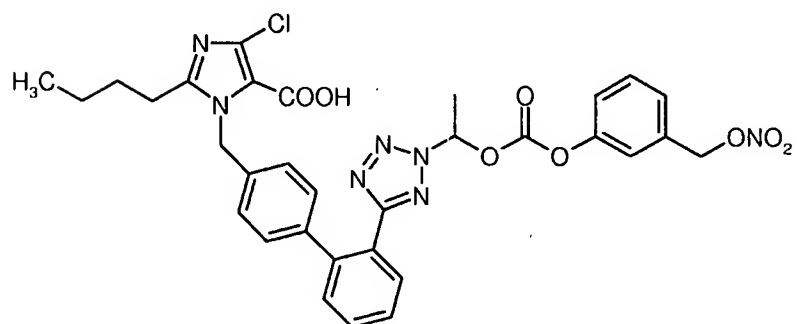
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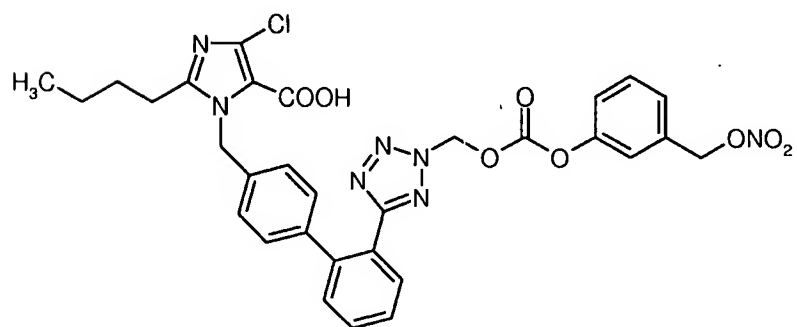
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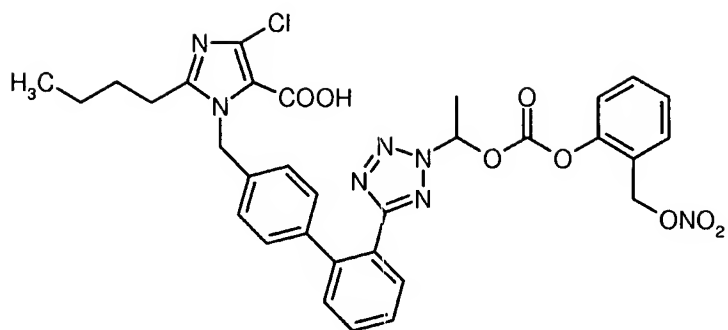
(169)



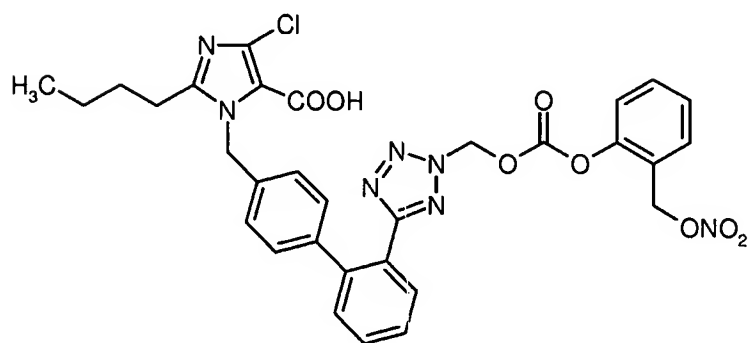
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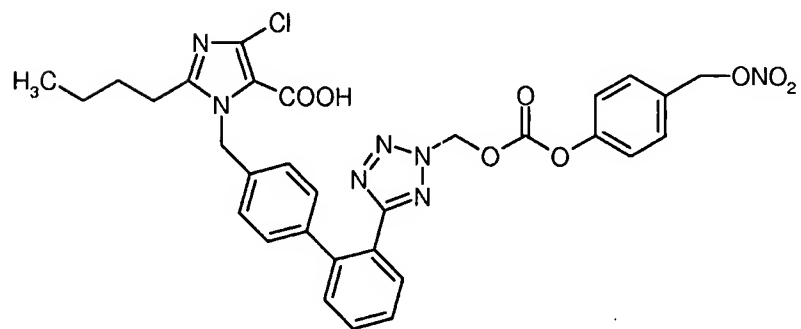
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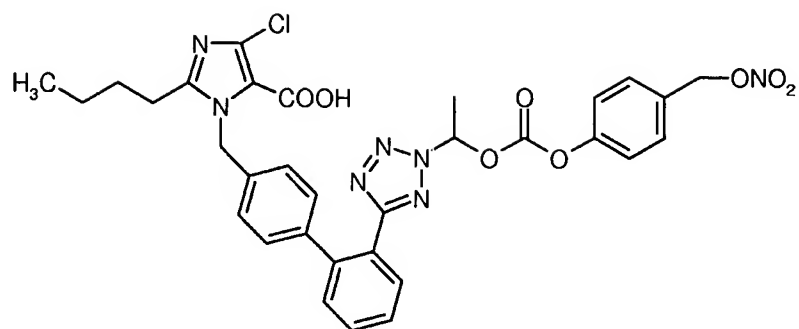
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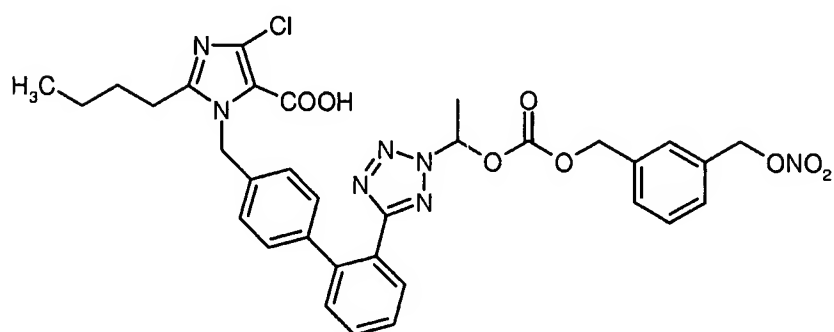
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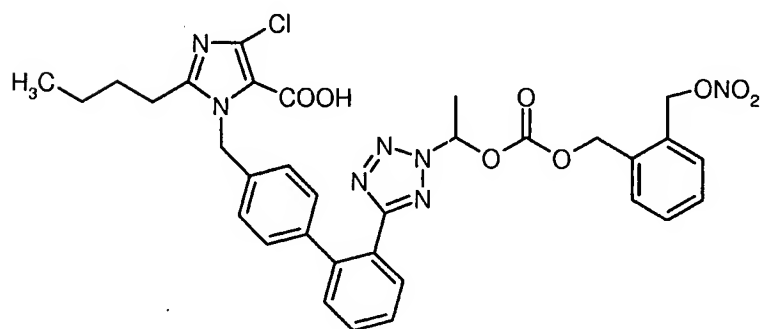
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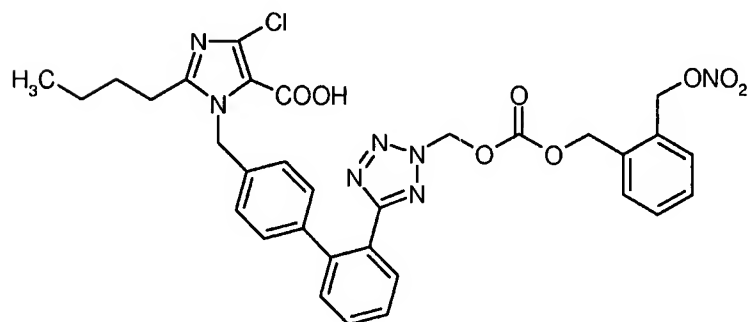
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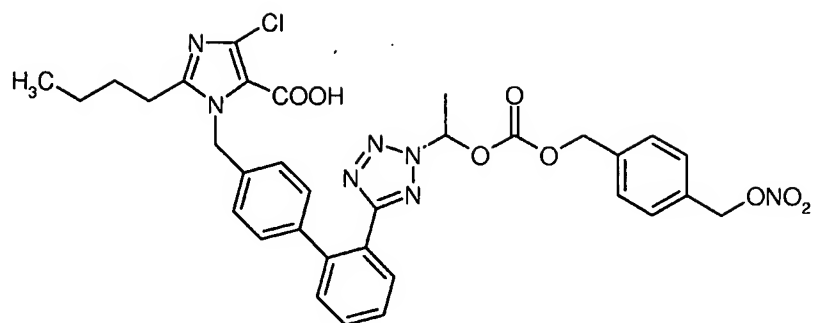
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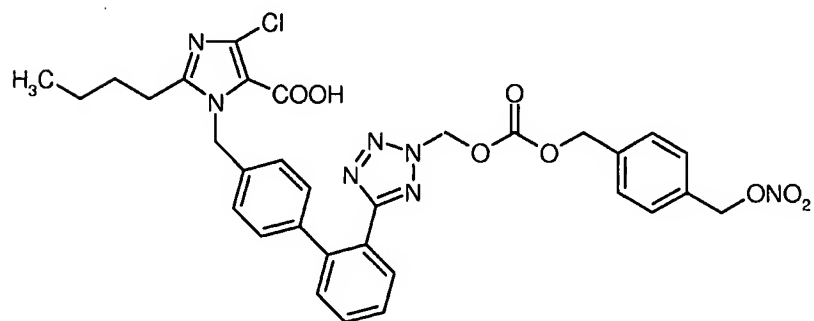
(177)



(178)

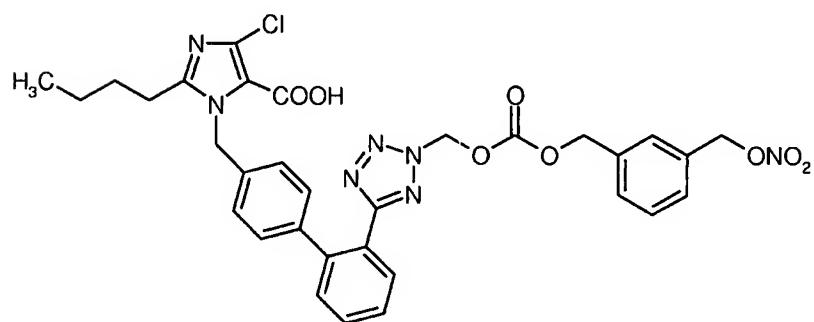


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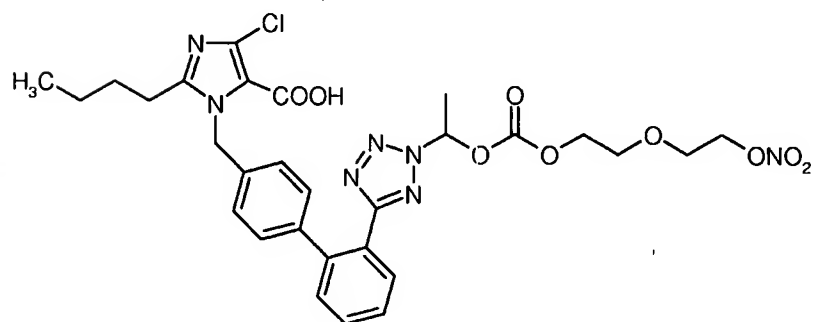


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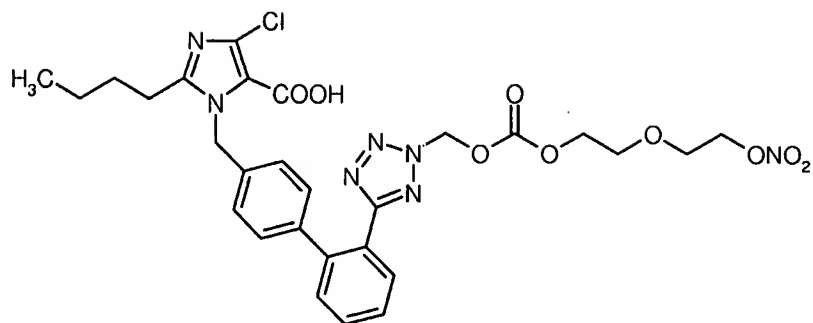
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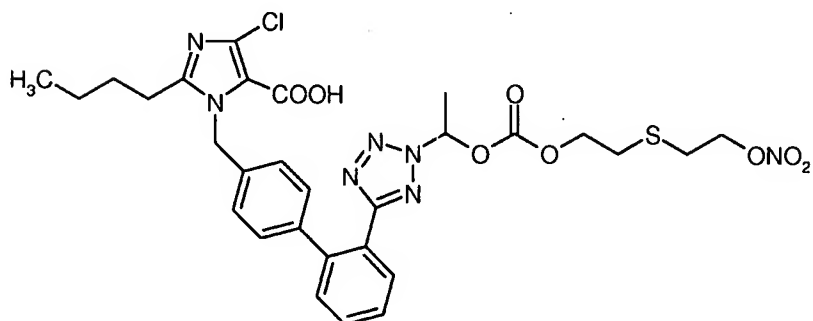
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(182)

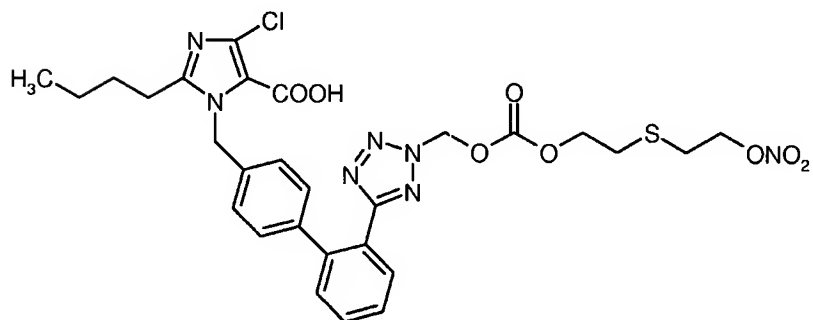


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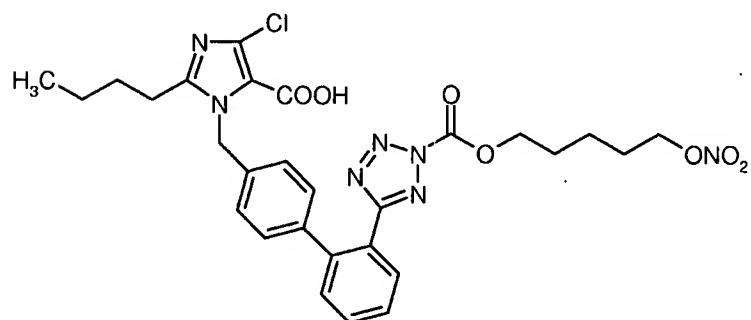


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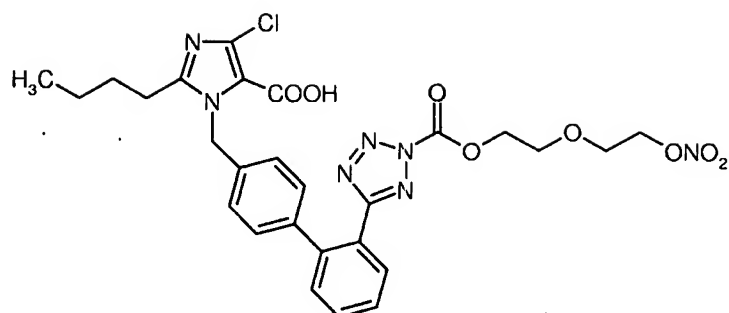
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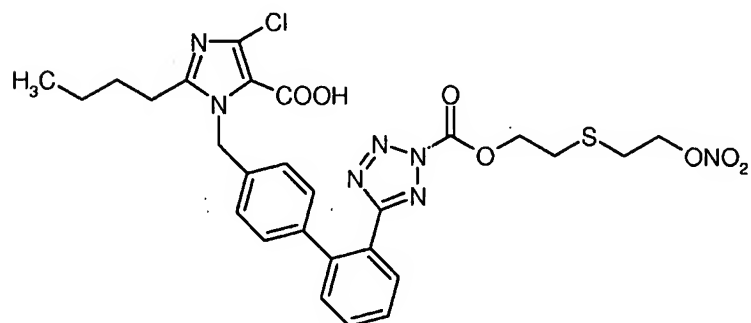
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(186)

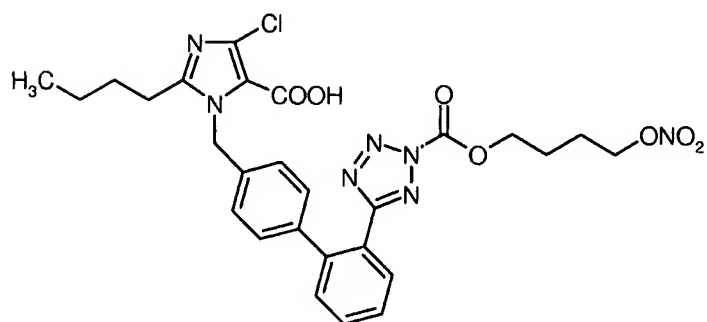


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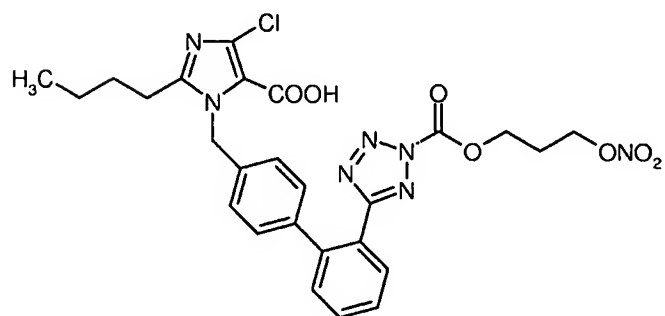


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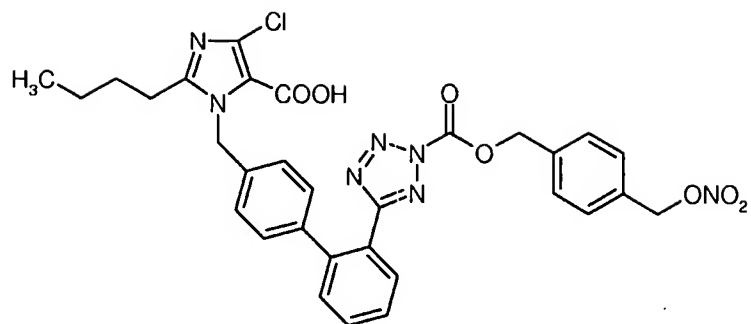
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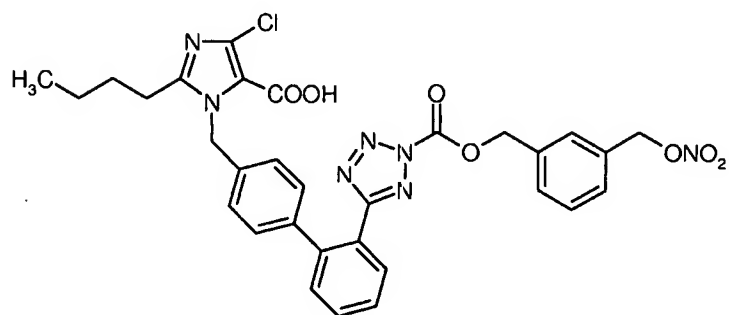
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(190)

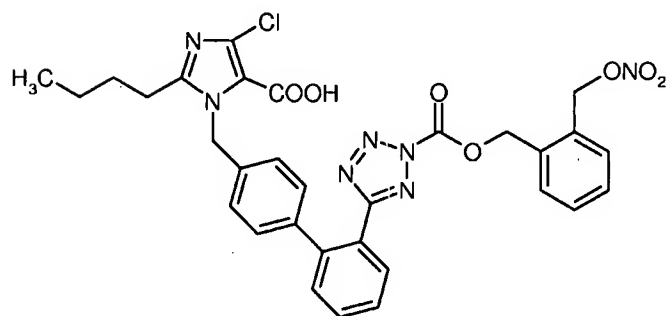


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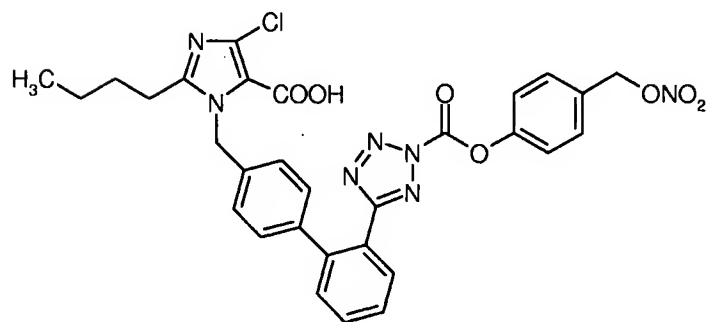


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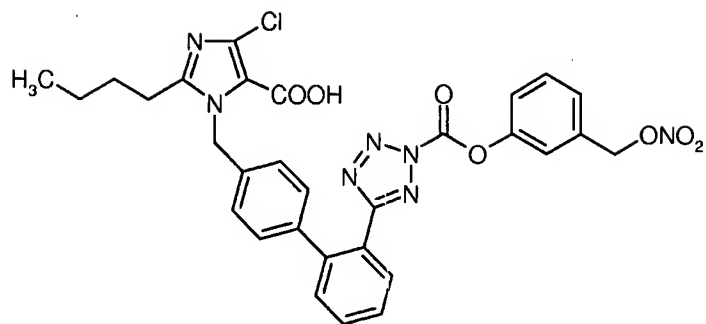
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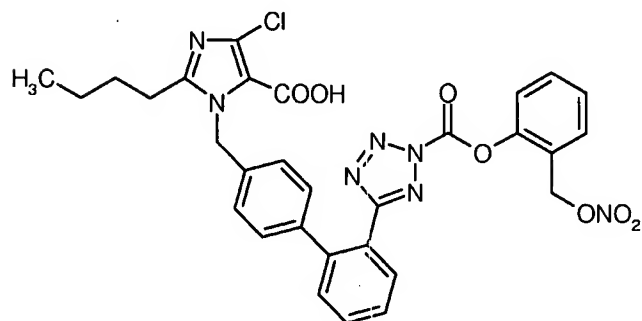
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(194)

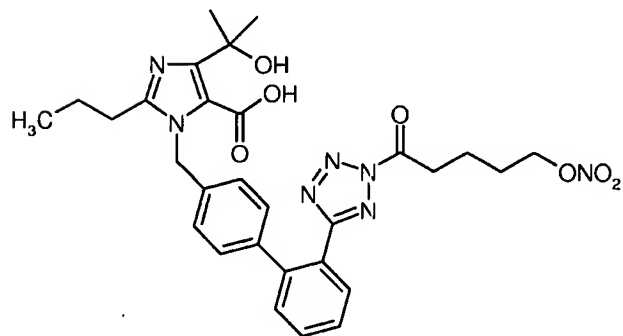


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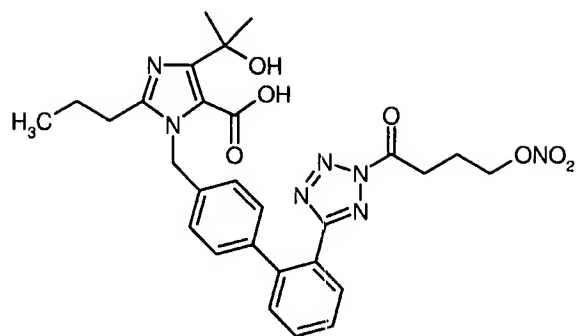


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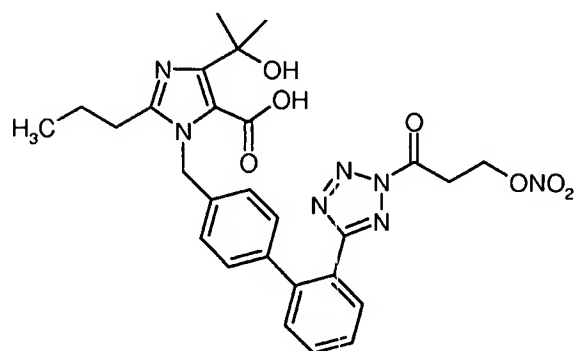
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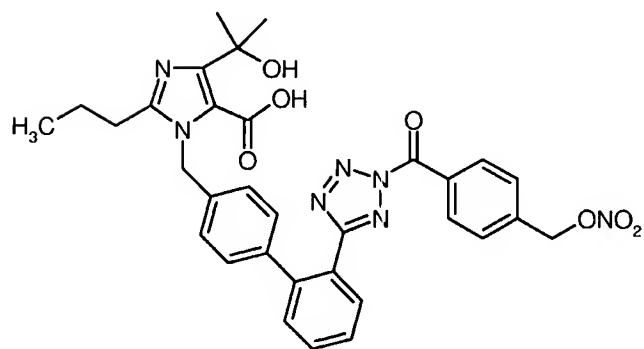
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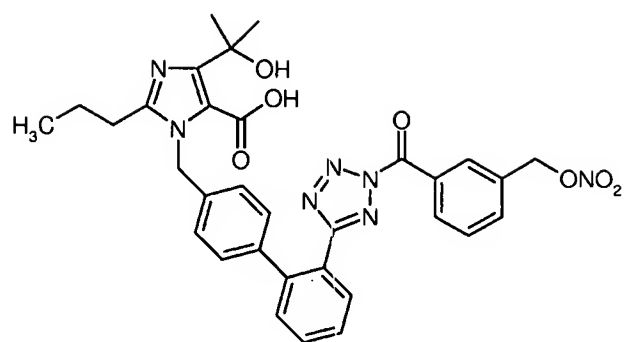
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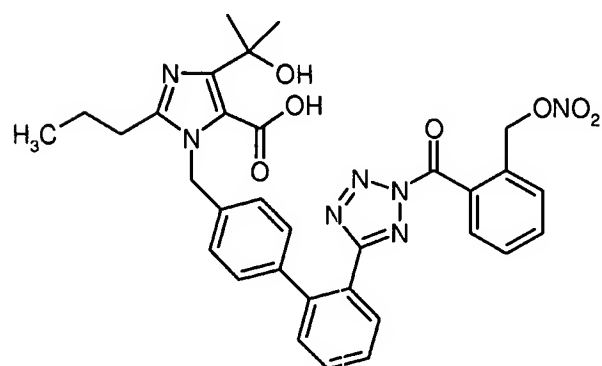
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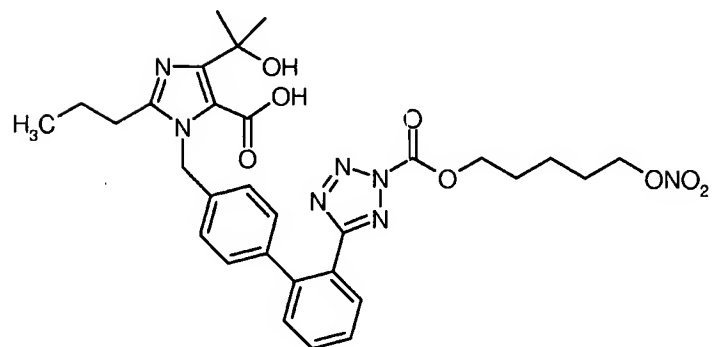
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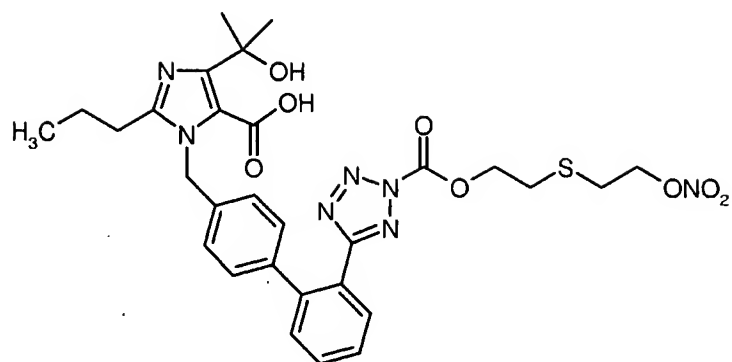
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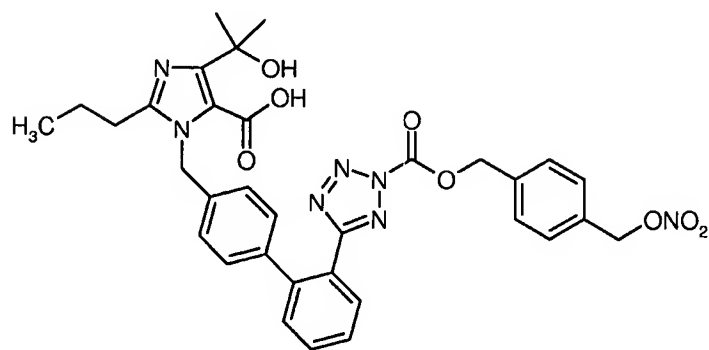
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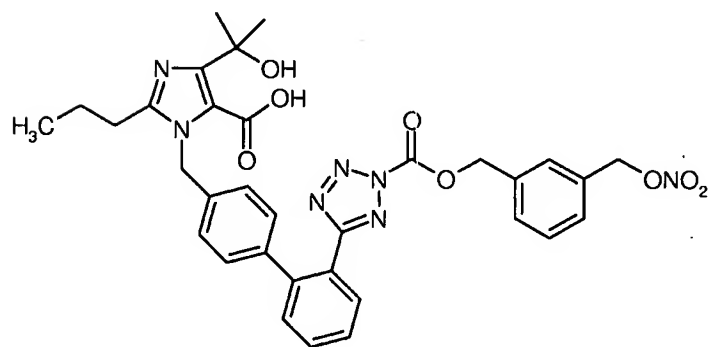
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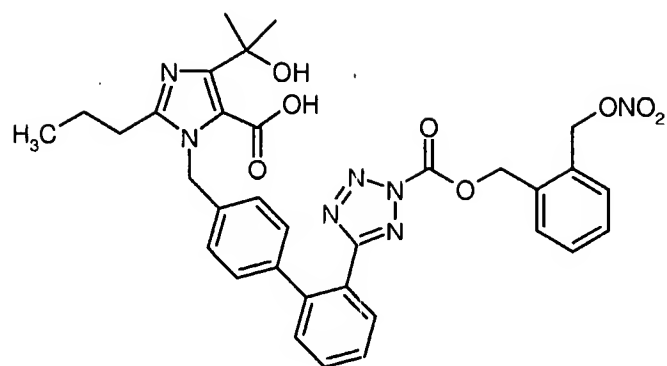
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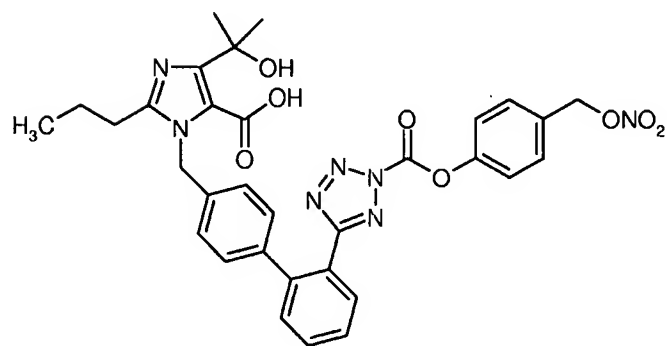
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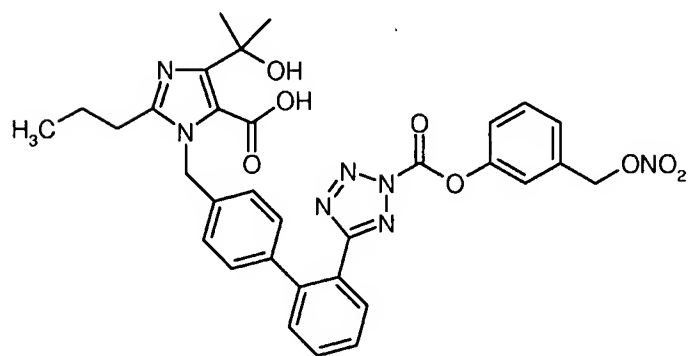
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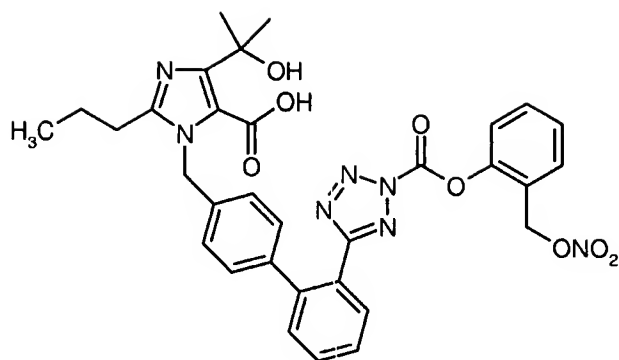
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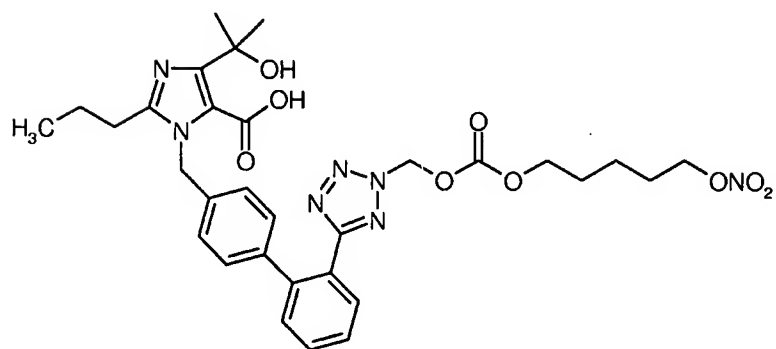
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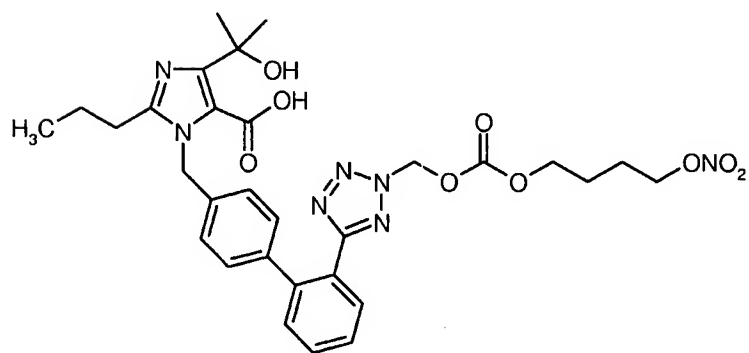
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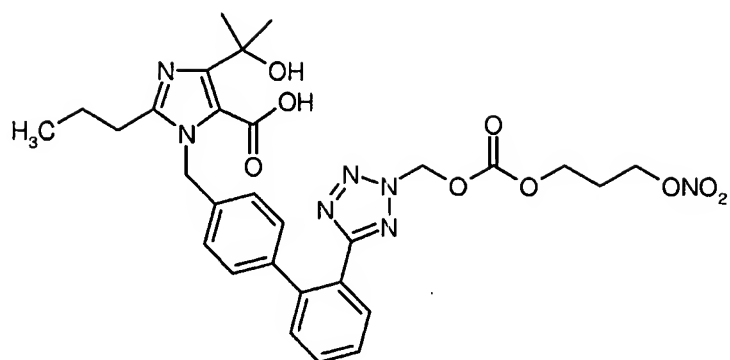
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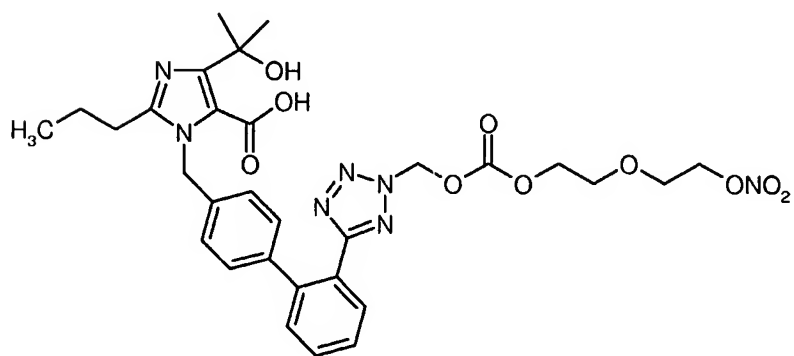
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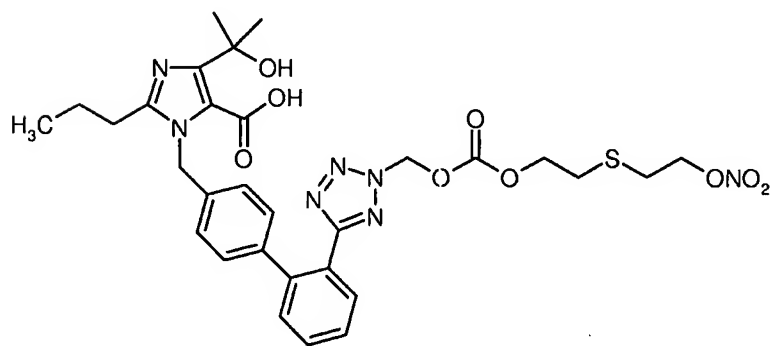
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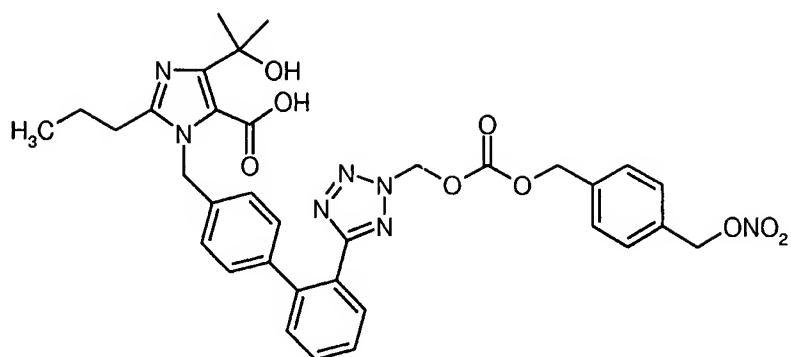
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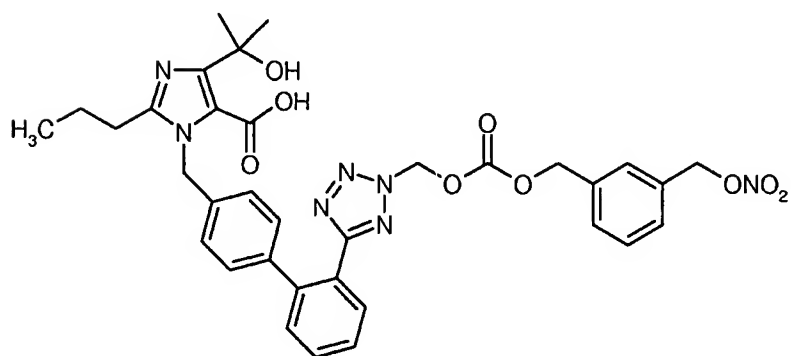
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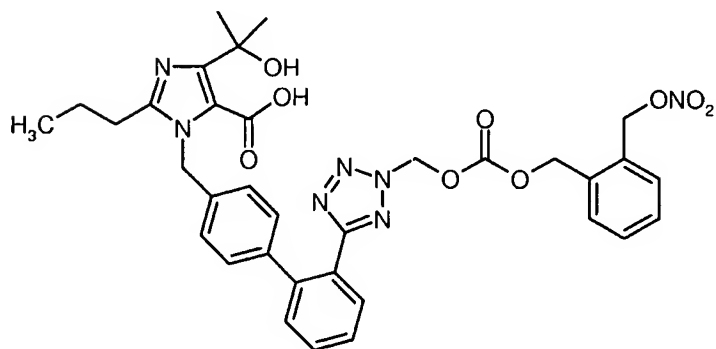
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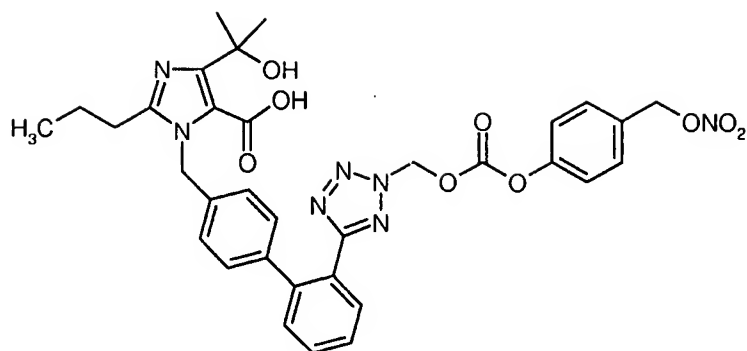
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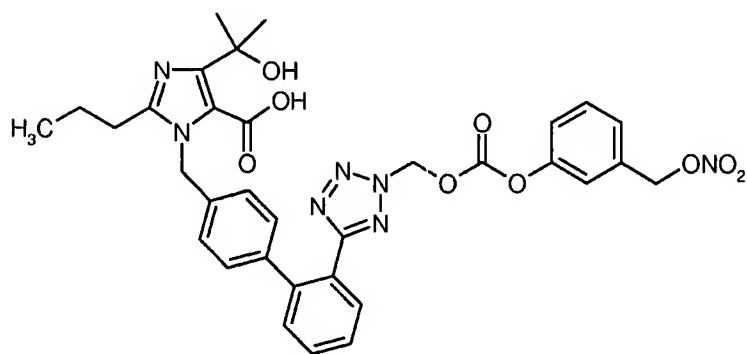
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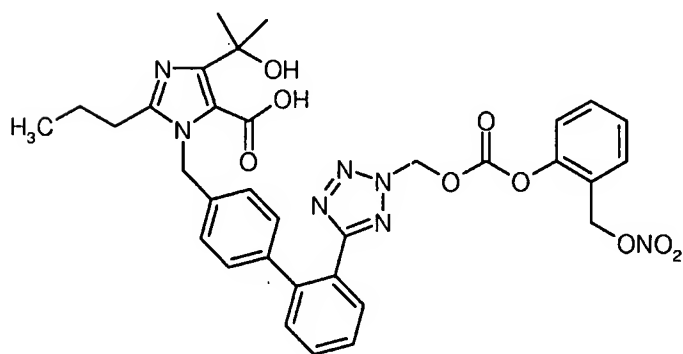
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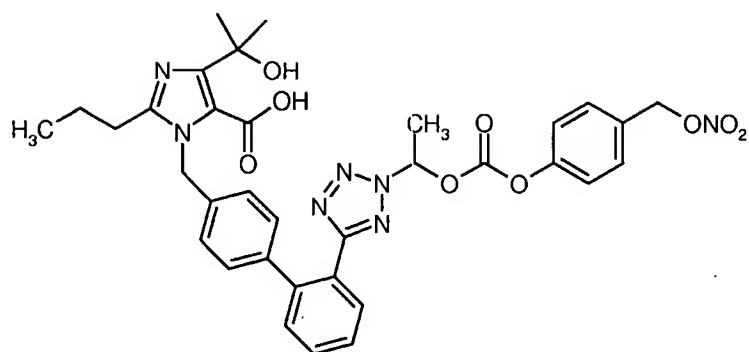
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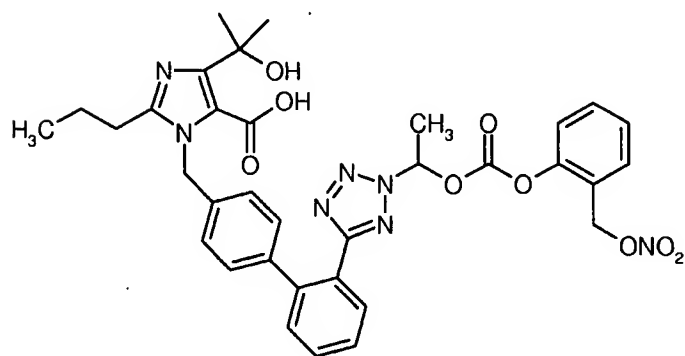
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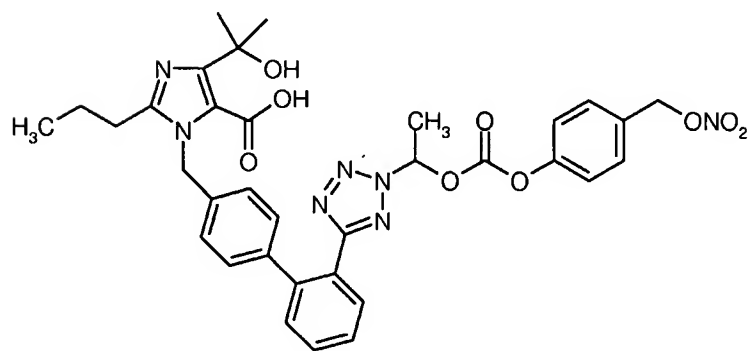
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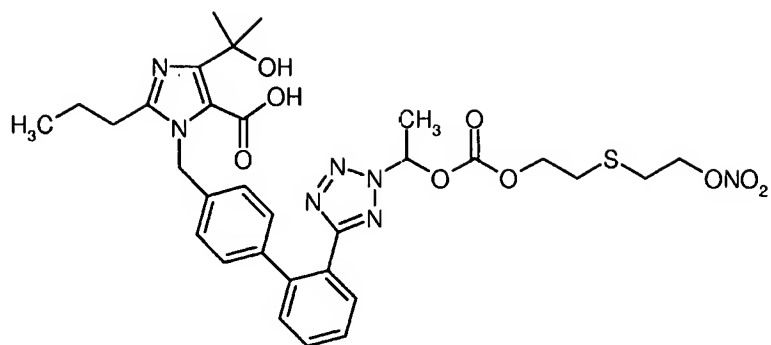
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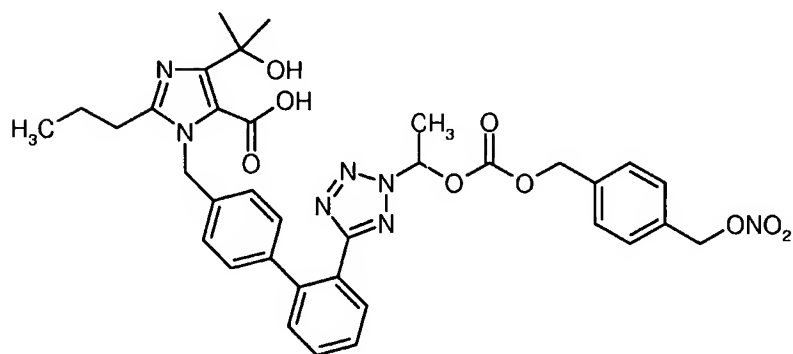
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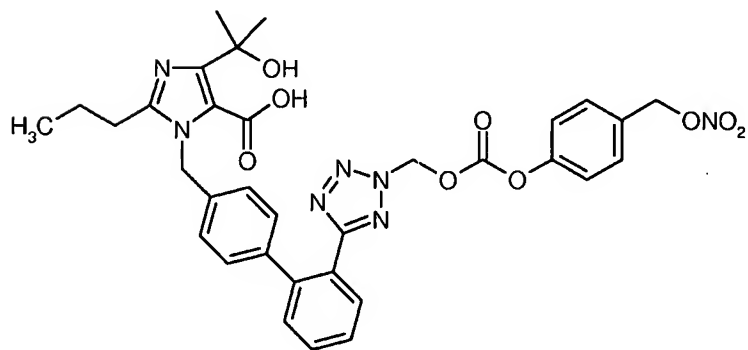
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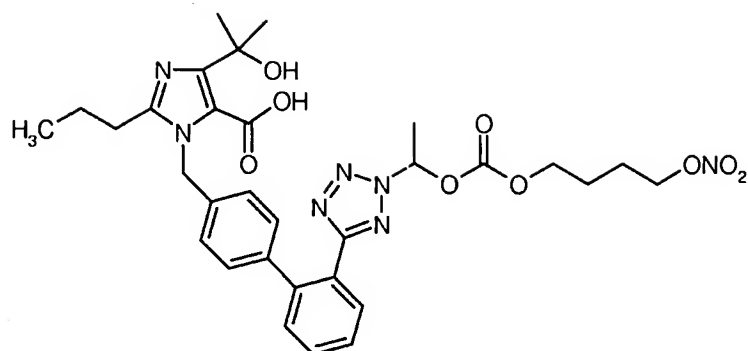
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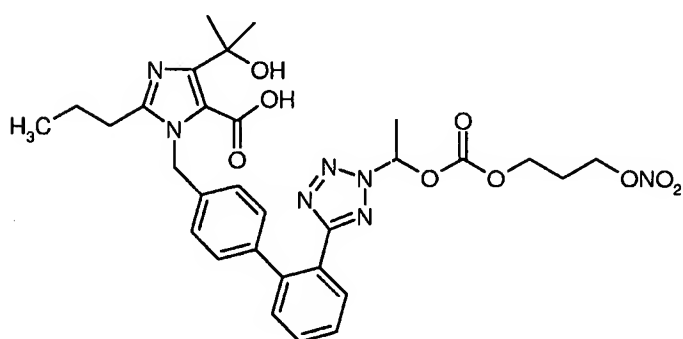
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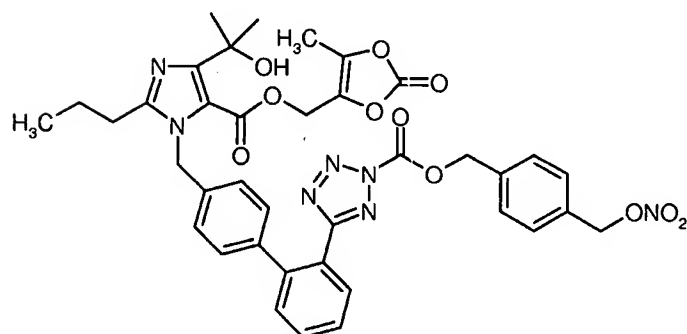
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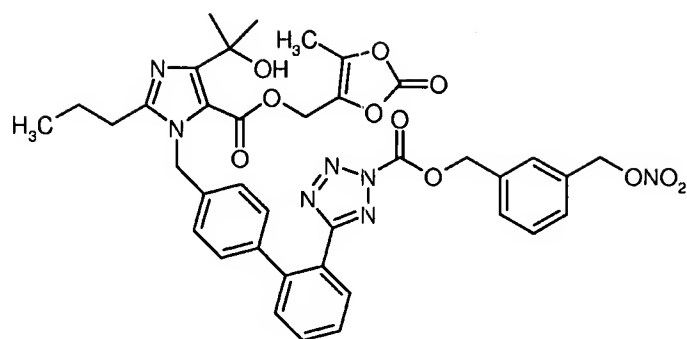
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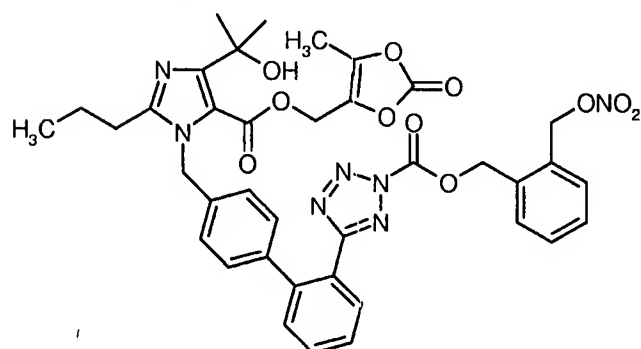
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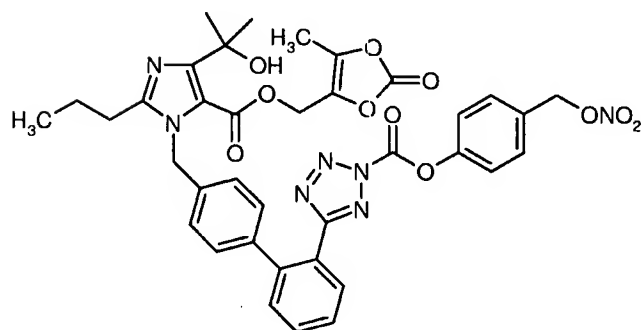
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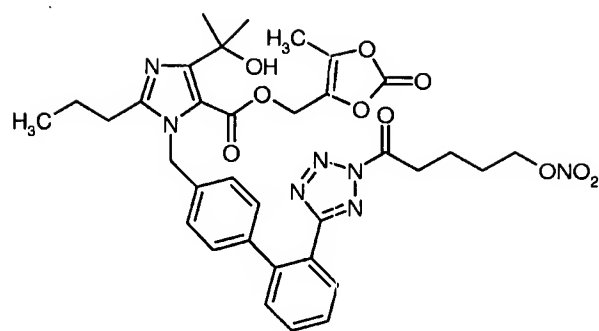
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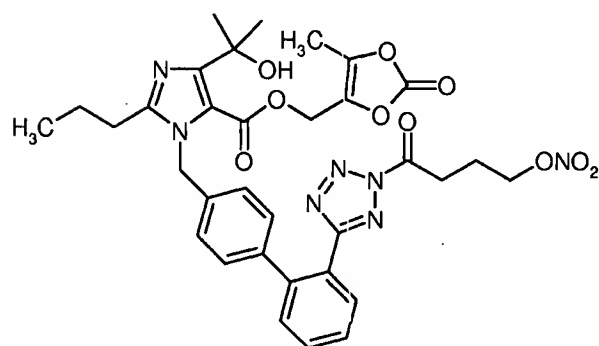
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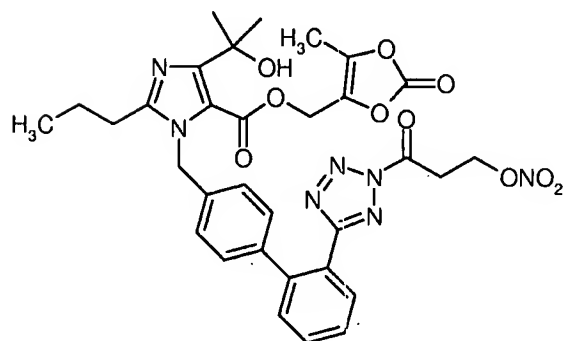
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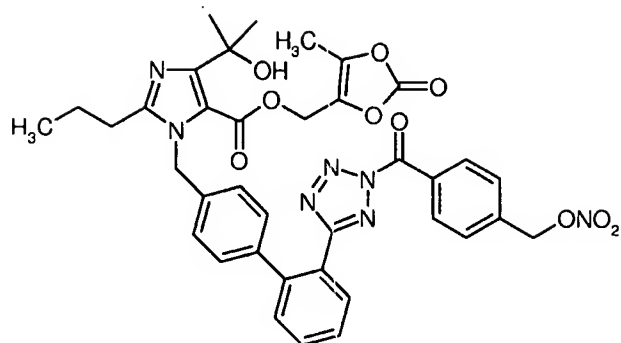
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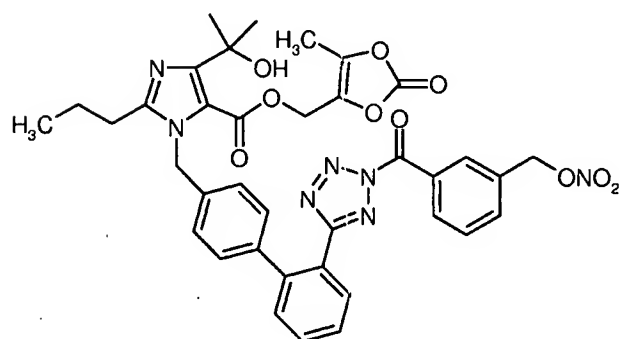
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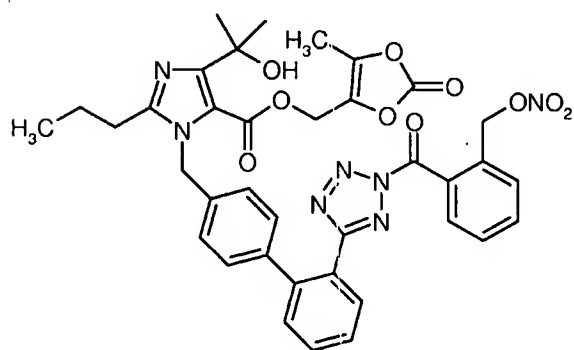
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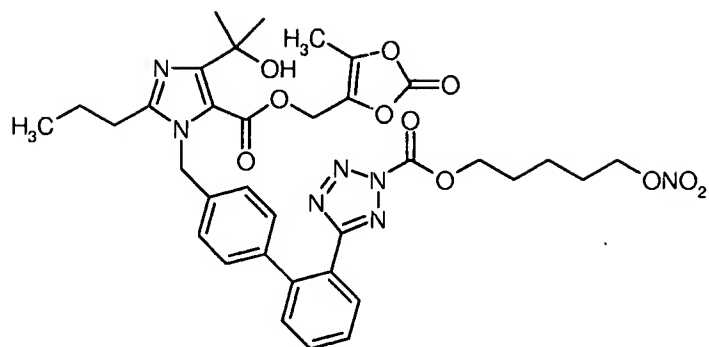
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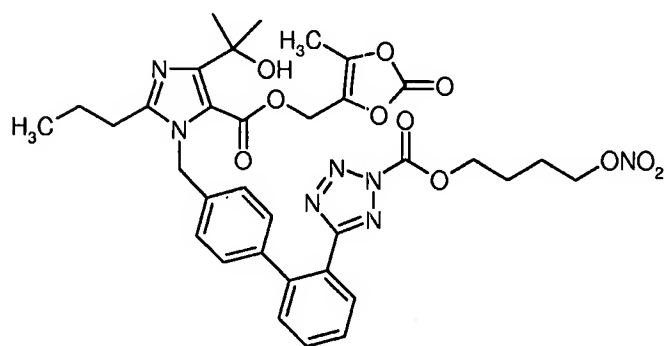
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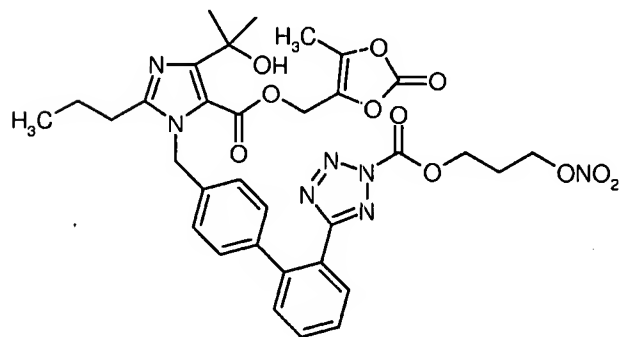
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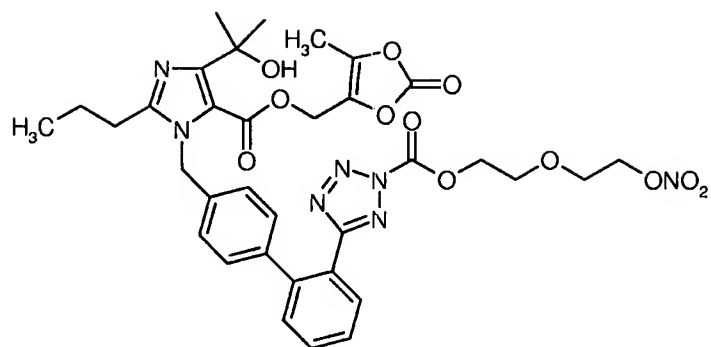
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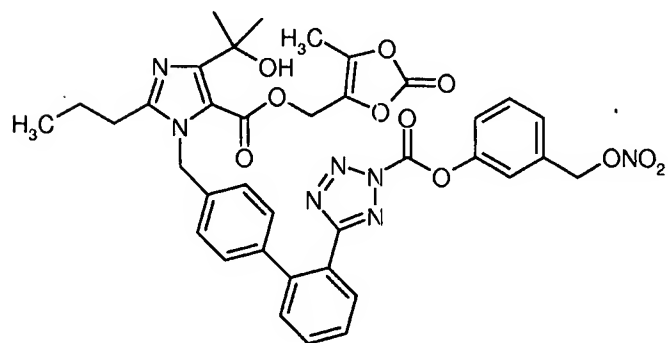
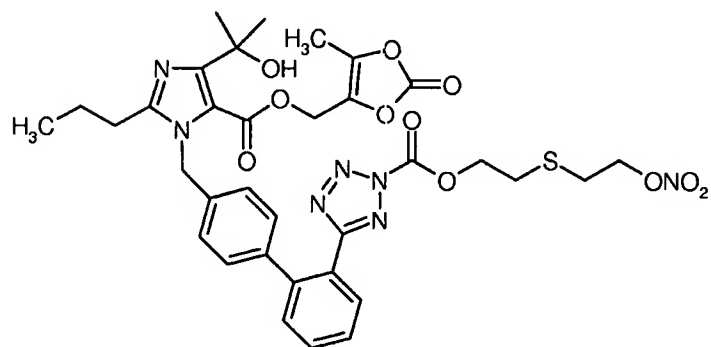
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(248)

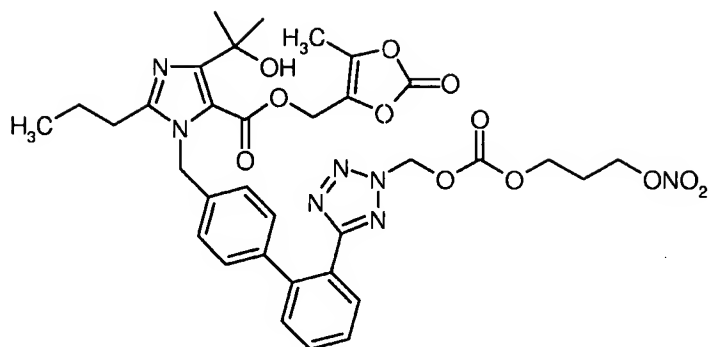


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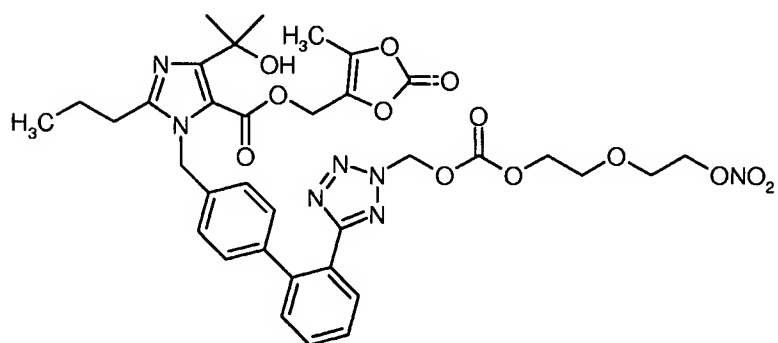


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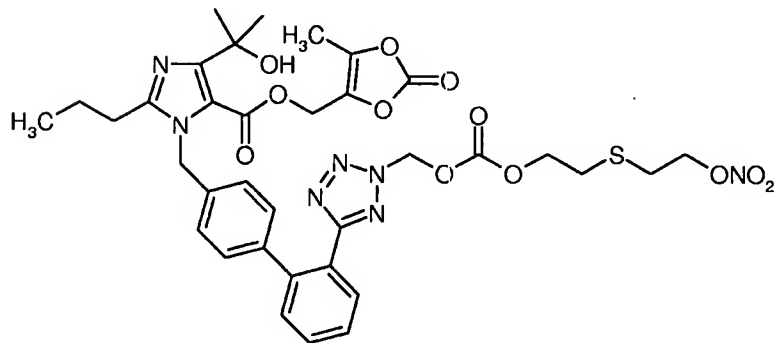




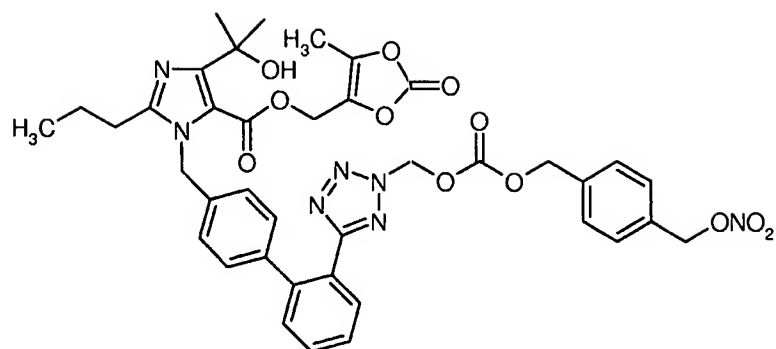
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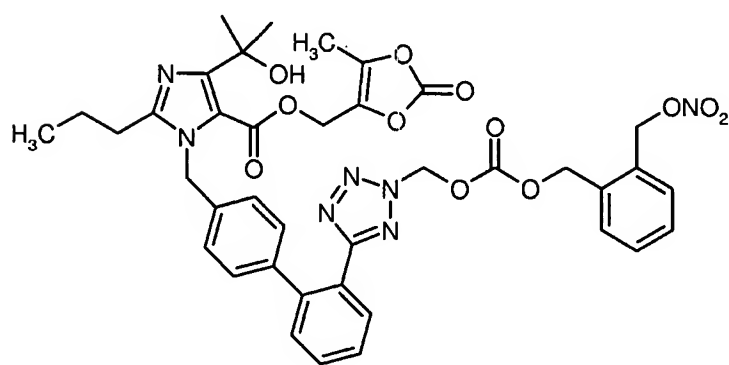
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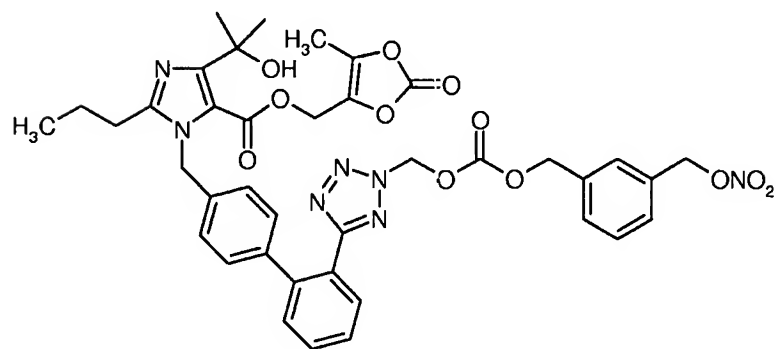
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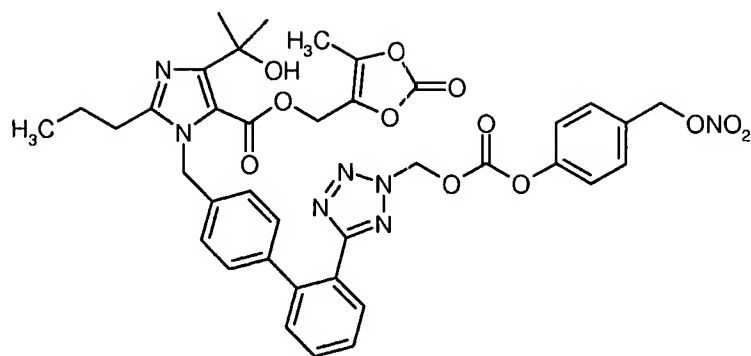
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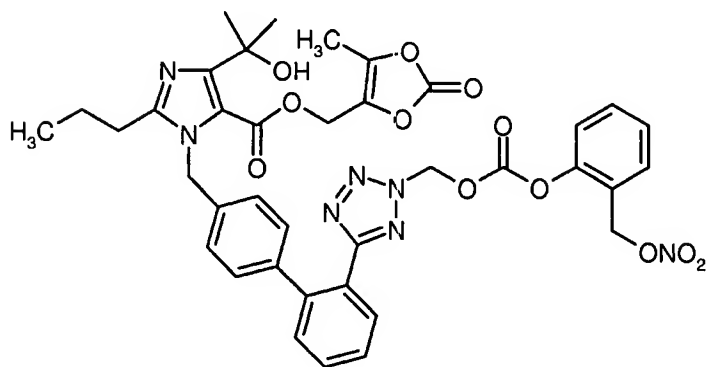
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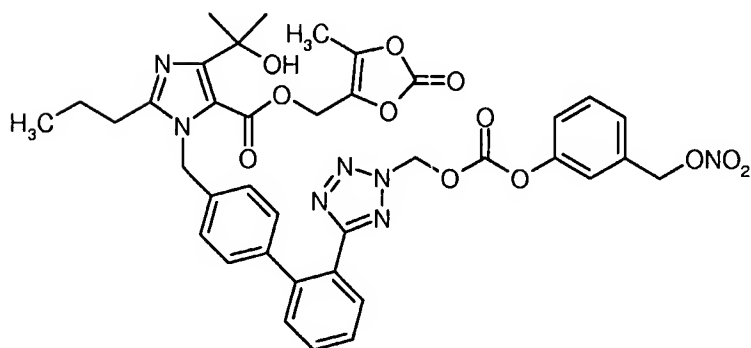
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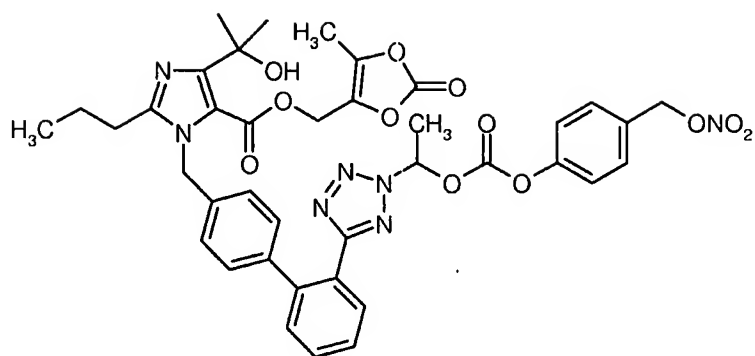
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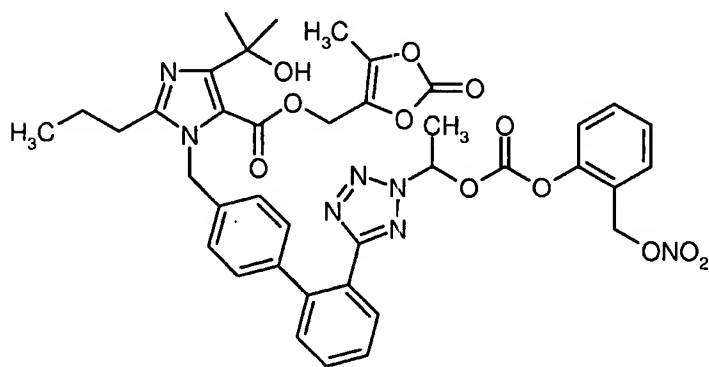
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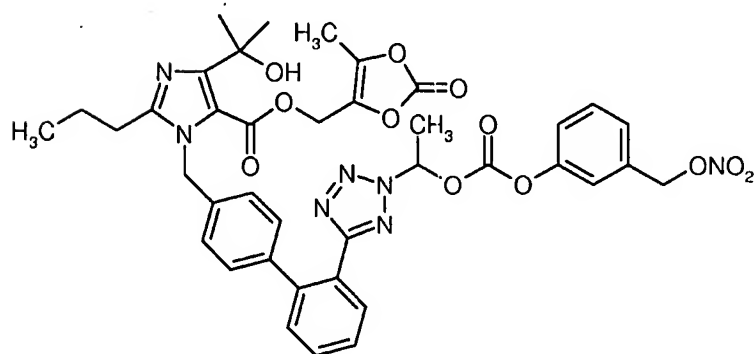
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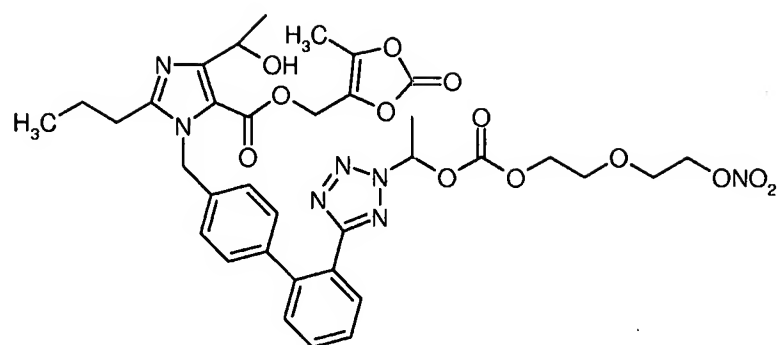
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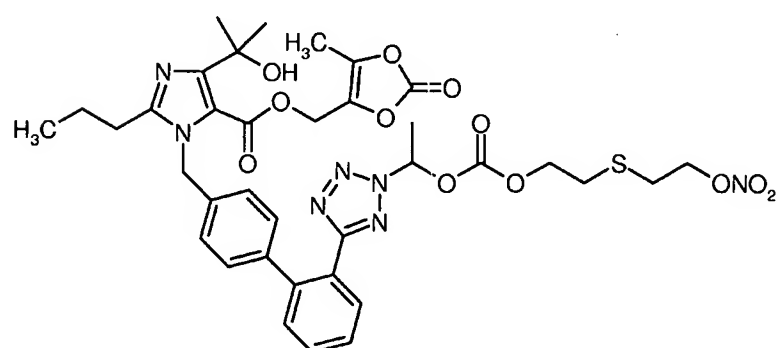
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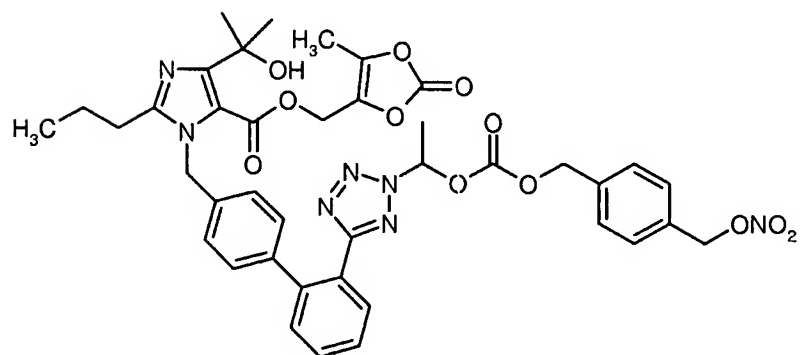
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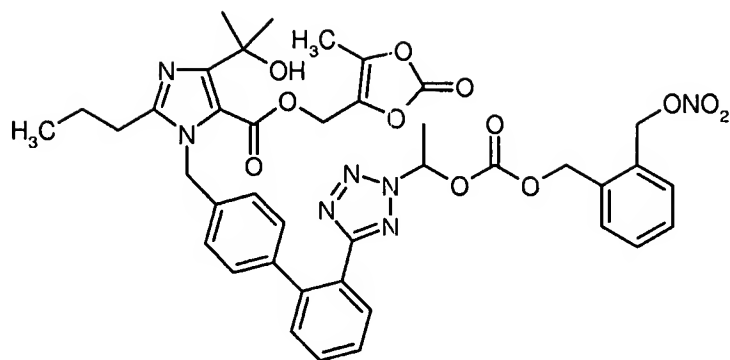
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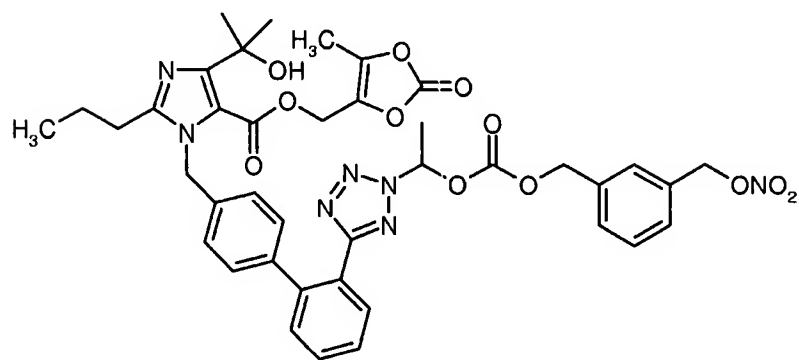
(268)



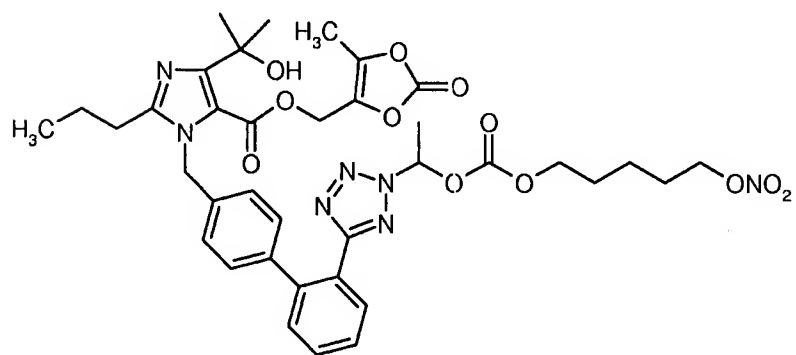
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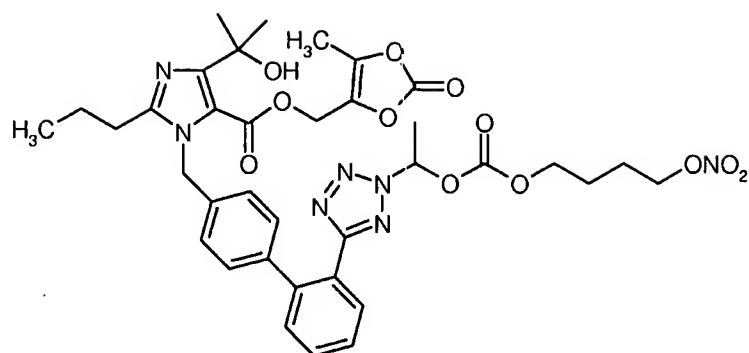
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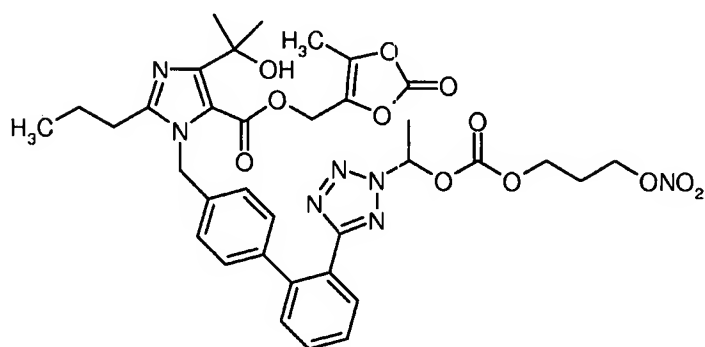
(271)



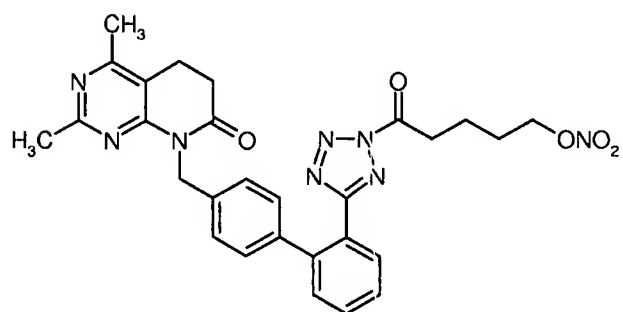
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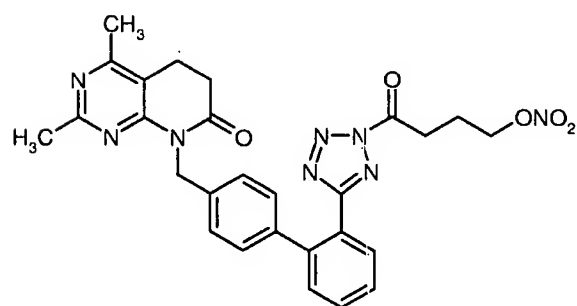
(273)



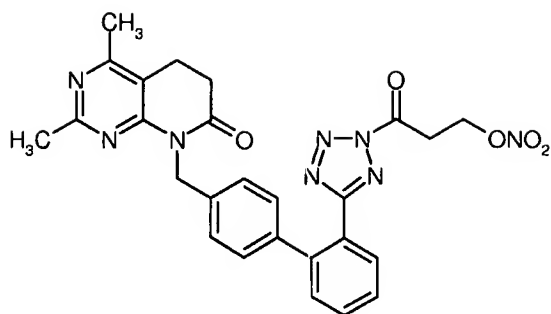
(274)



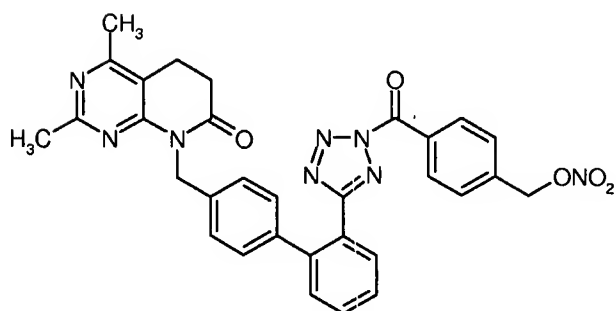
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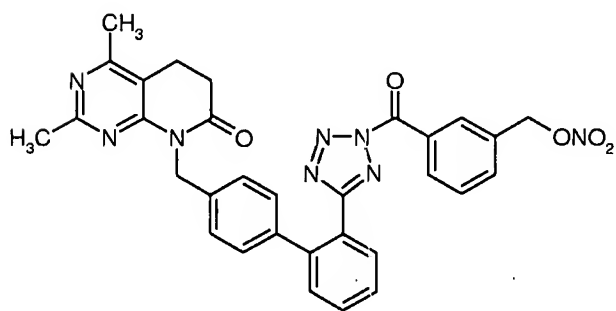
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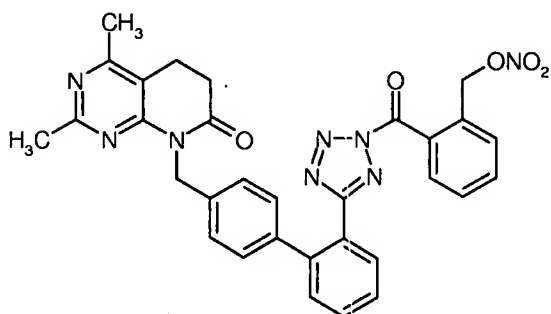
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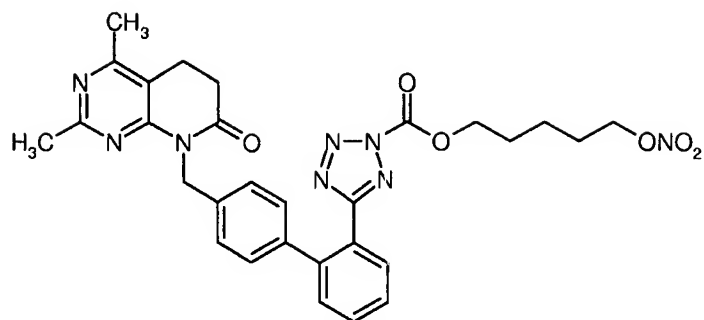
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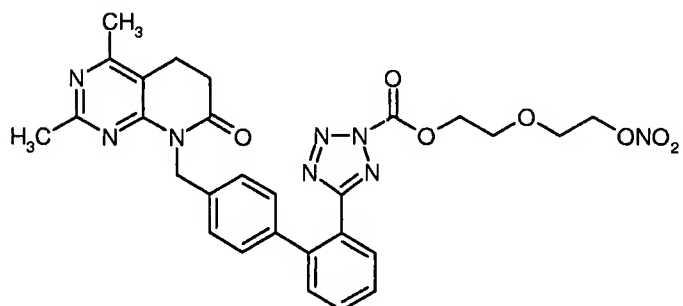
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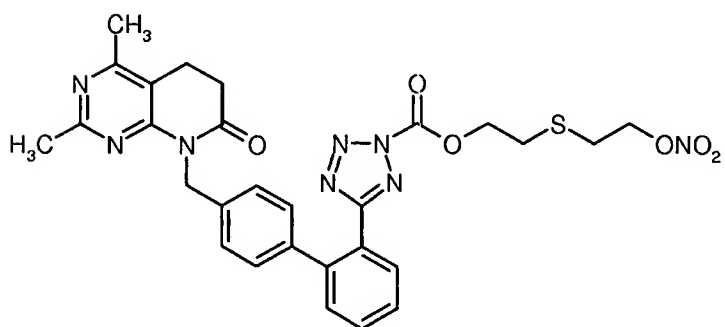
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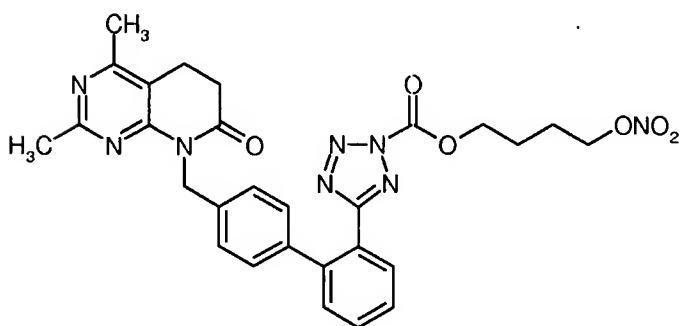
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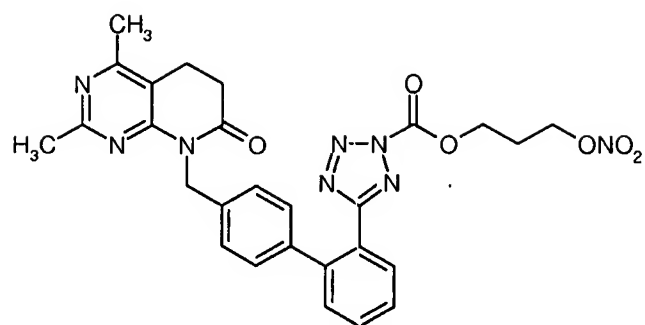
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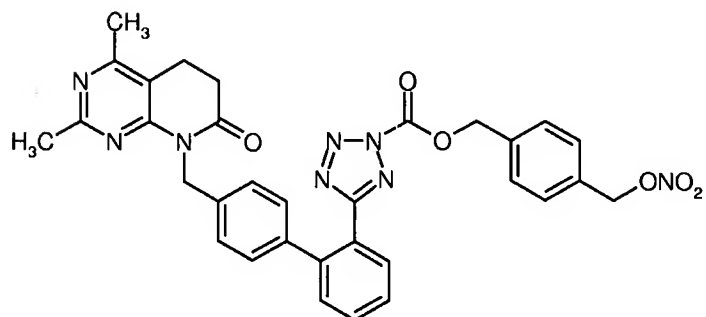
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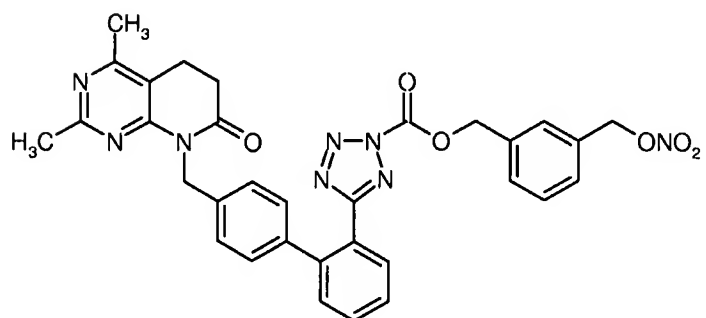
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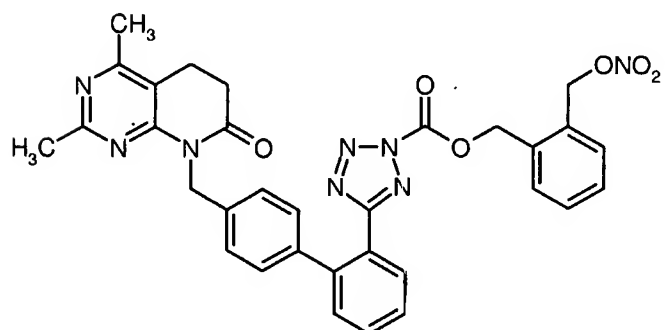
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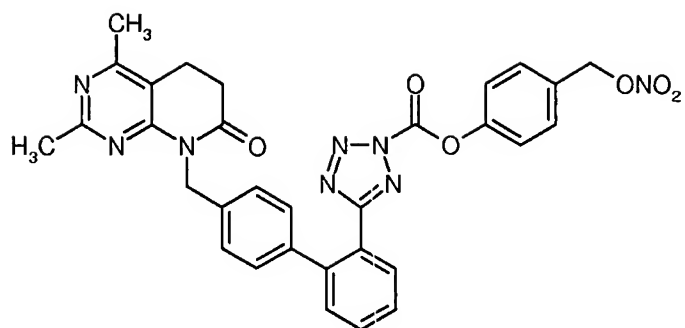
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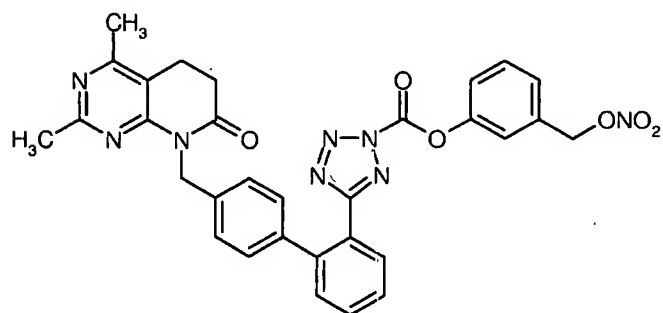
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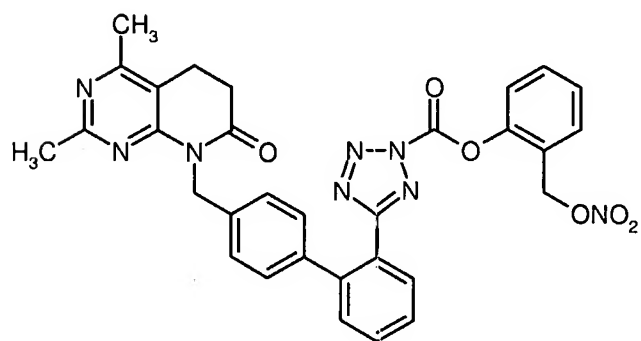


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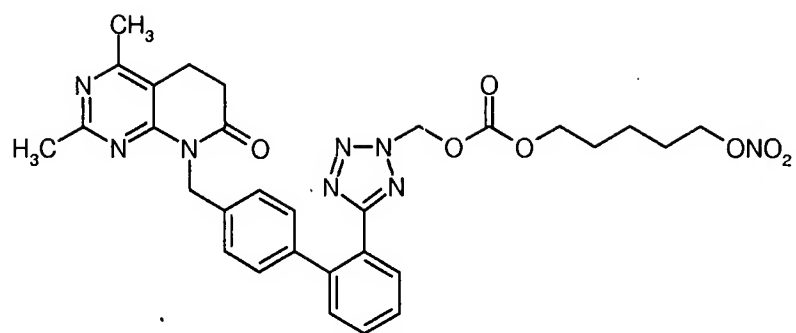


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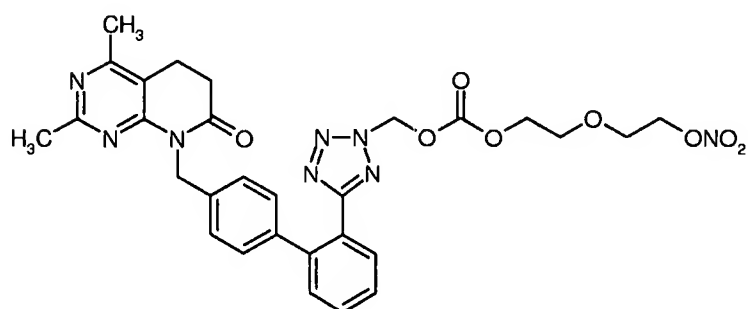
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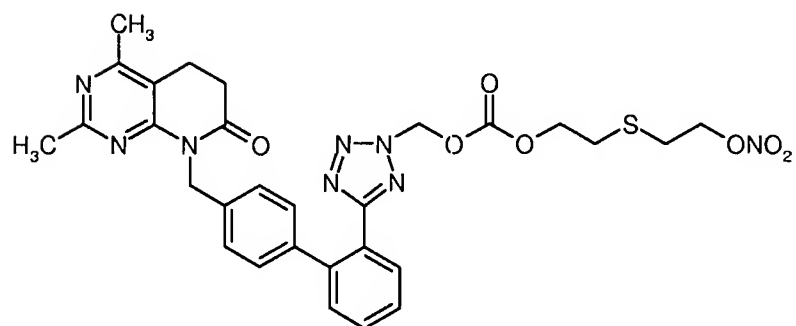
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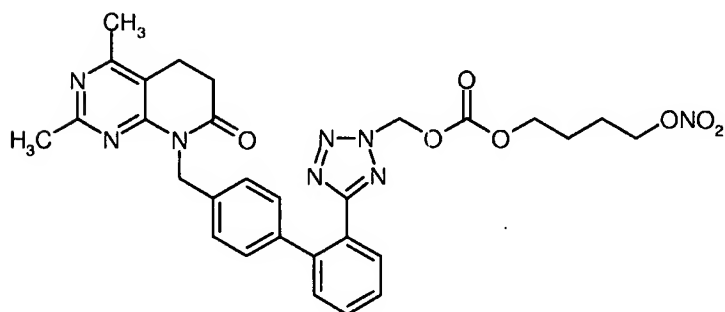
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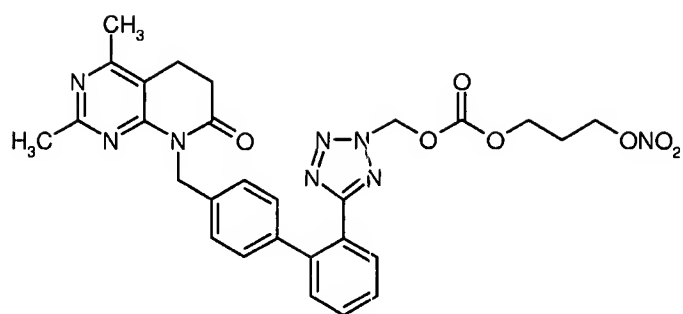
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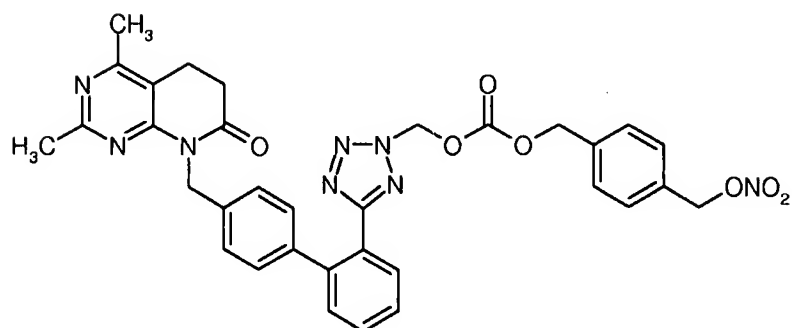
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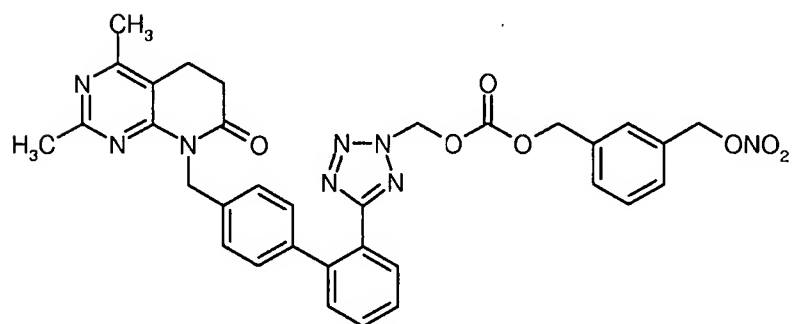
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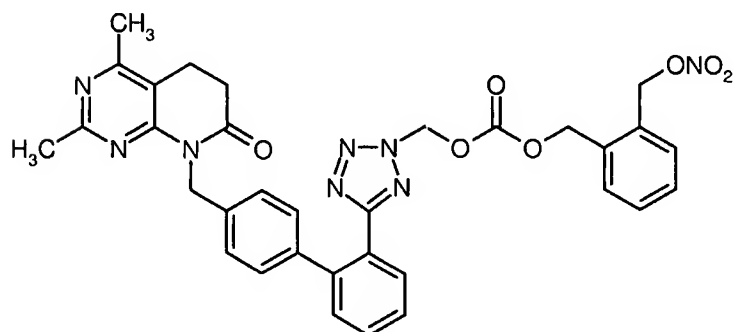
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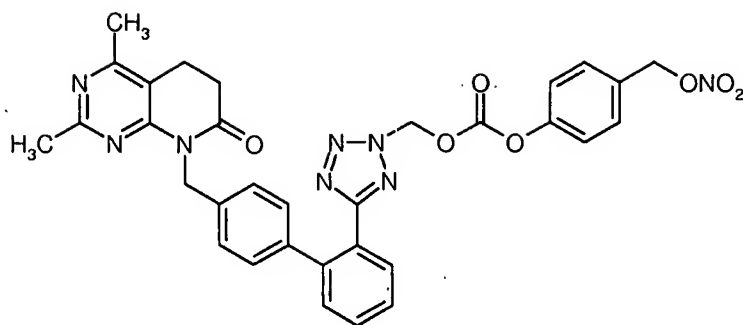
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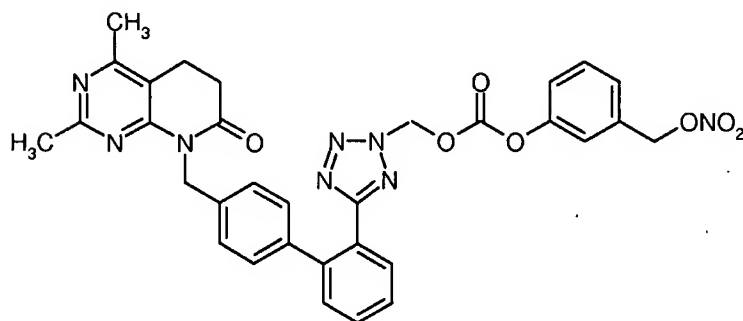
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(299)

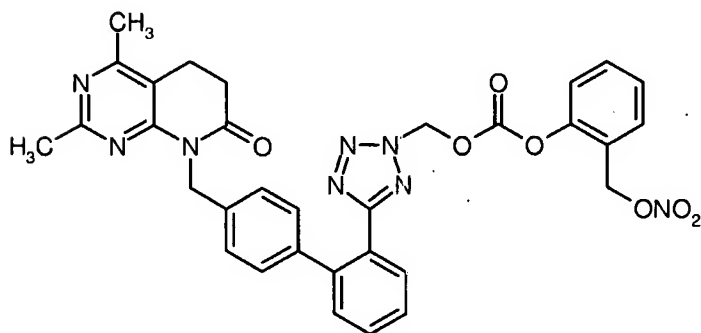


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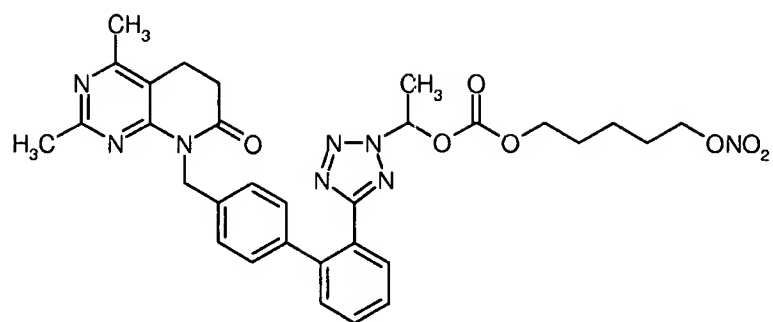


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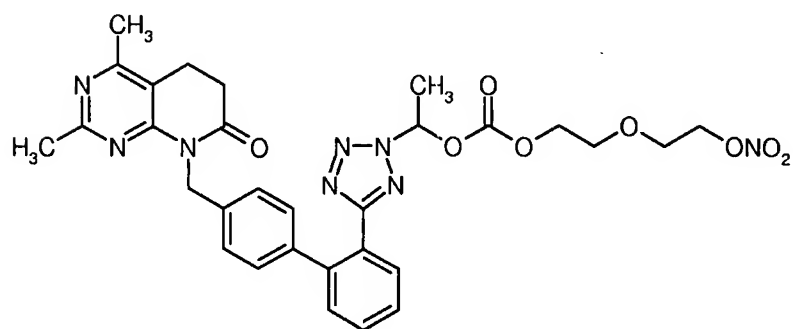
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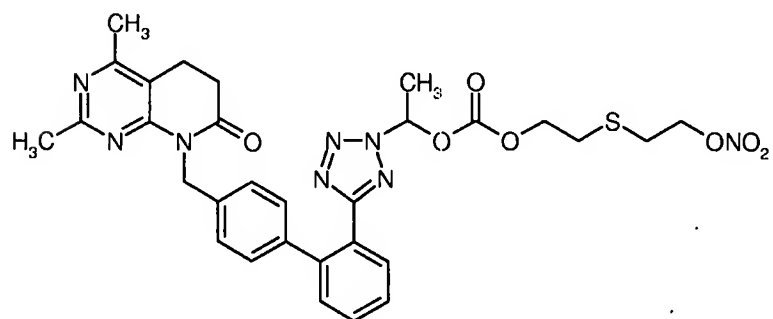
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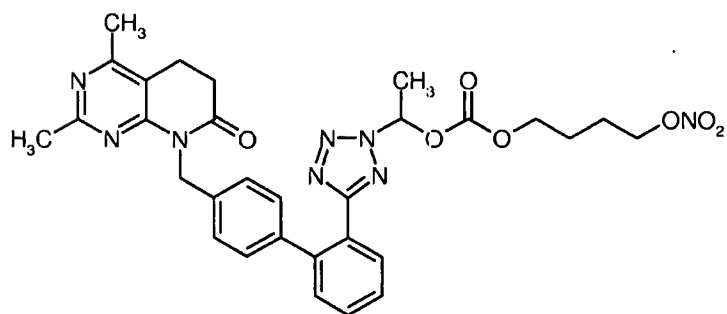
(303)



(304)

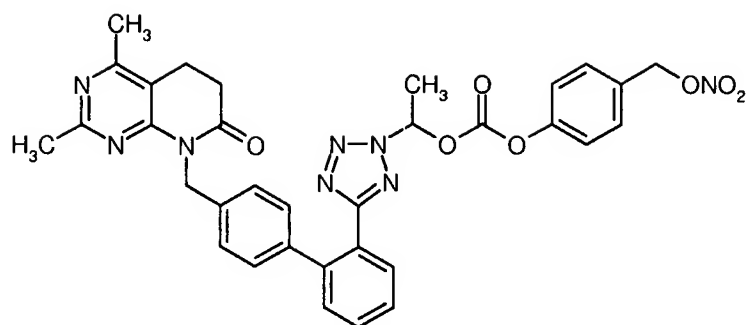


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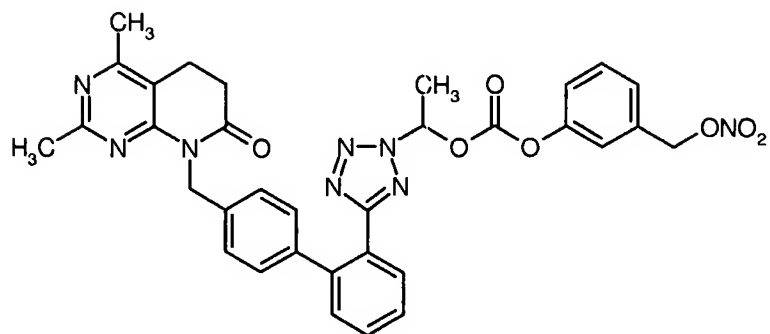


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(310)

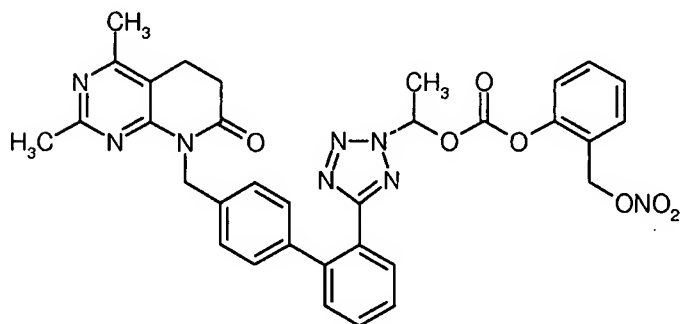


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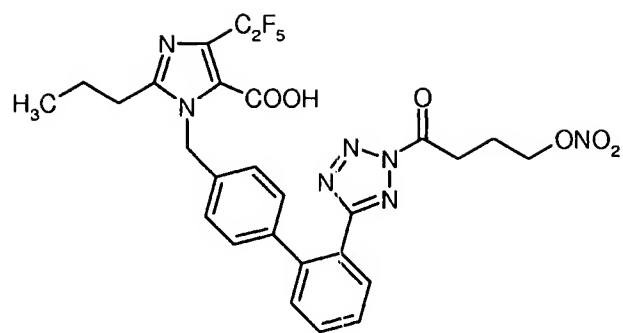


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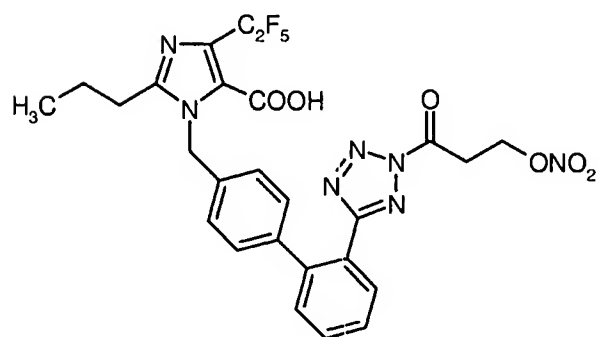
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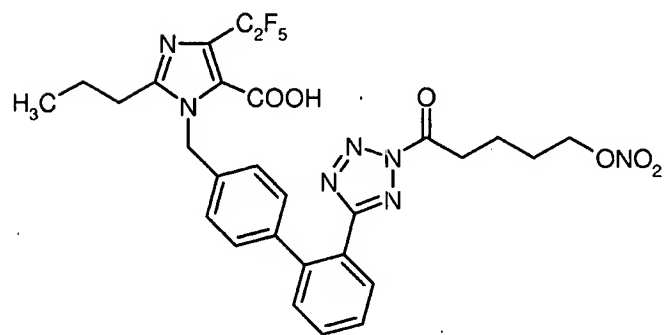
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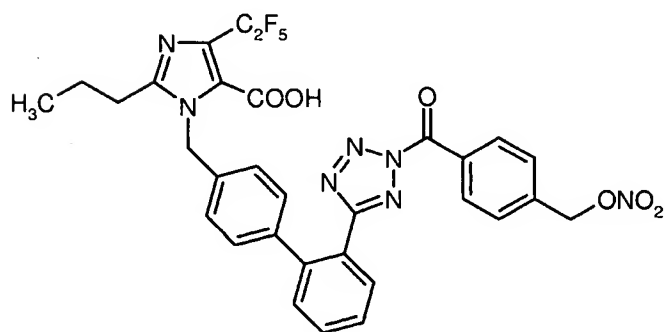
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(315)

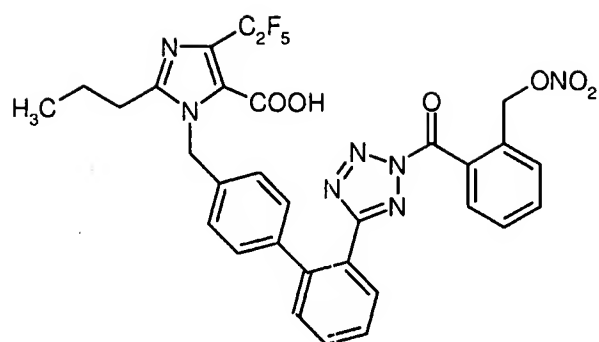


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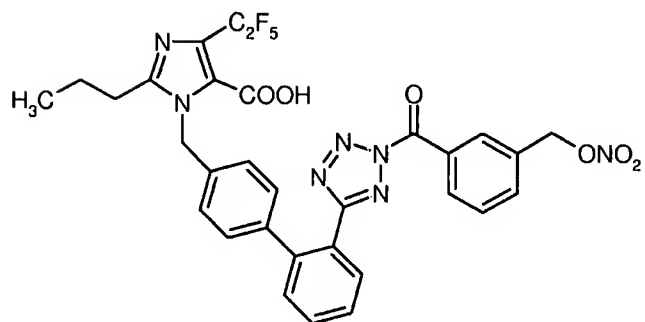


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(317)

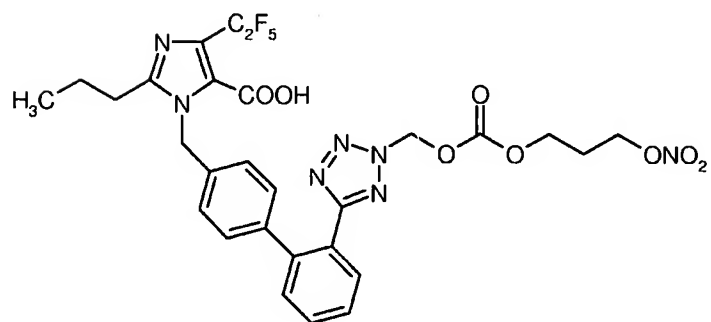


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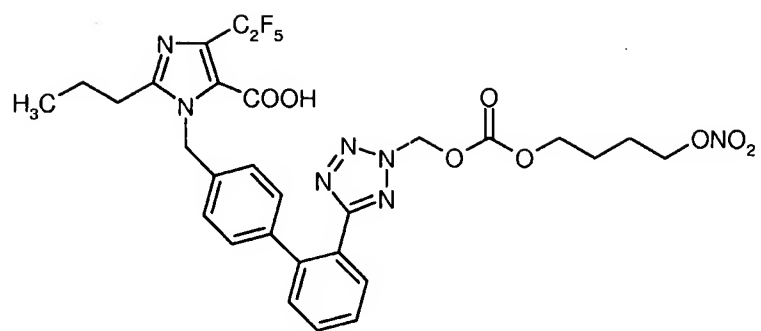


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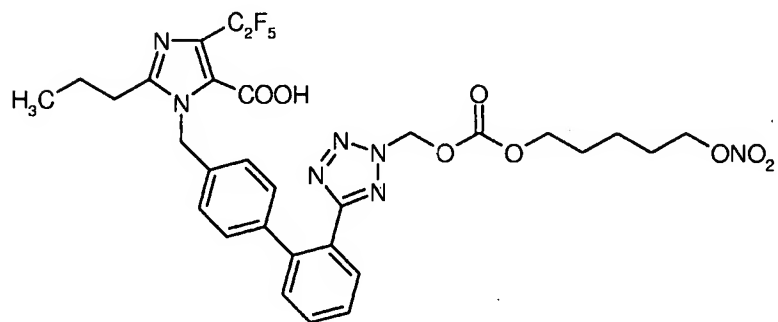
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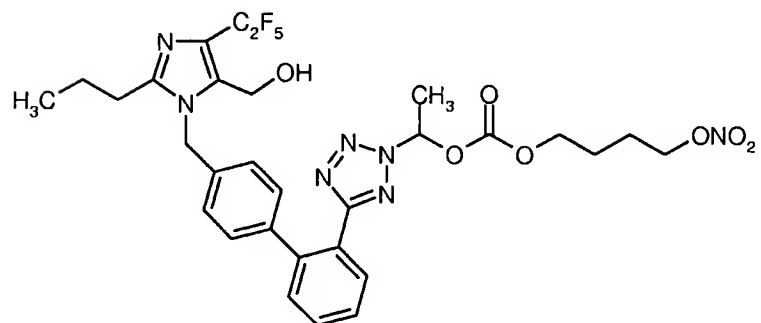
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(321)

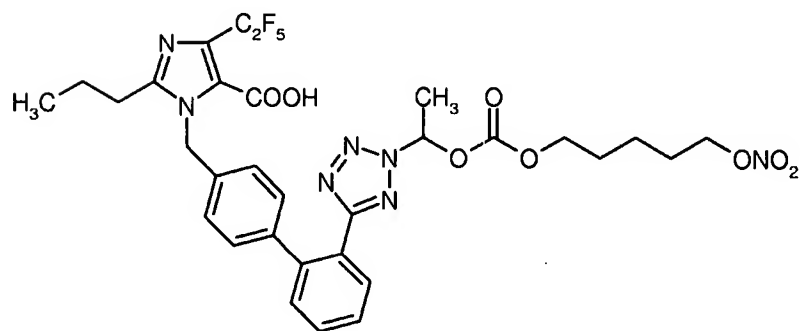


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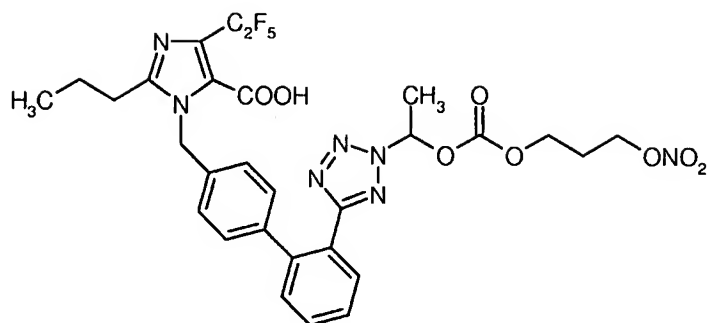


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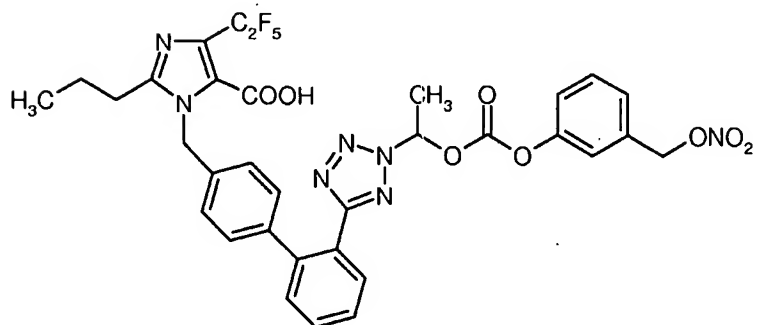
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(324)

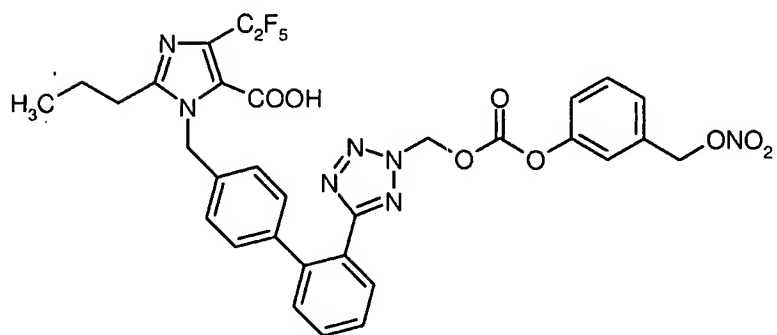


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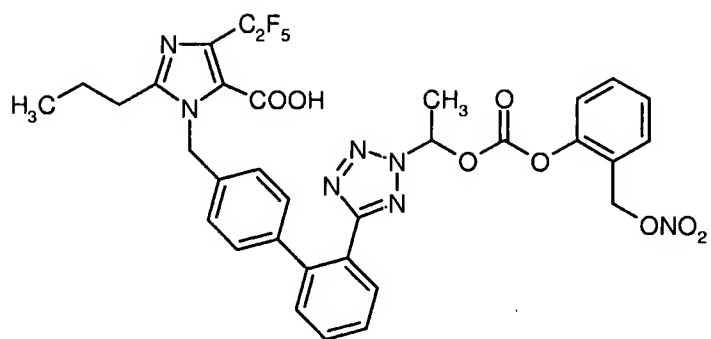


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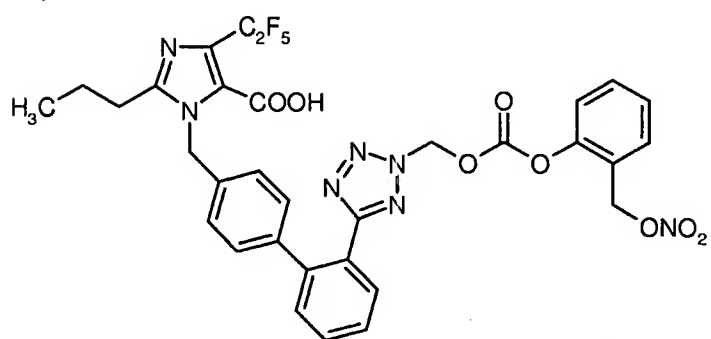
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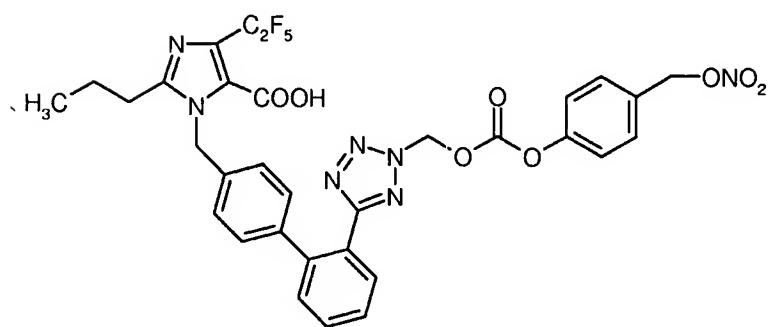
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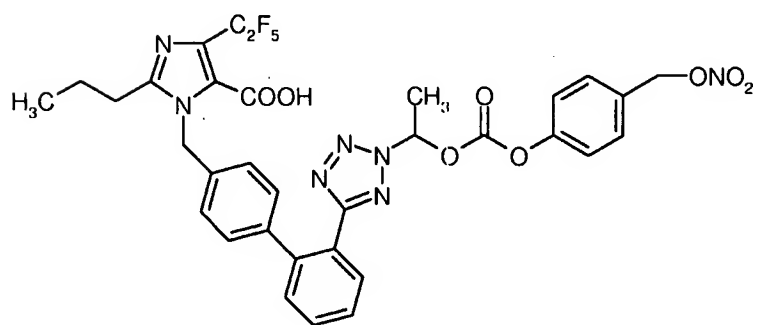
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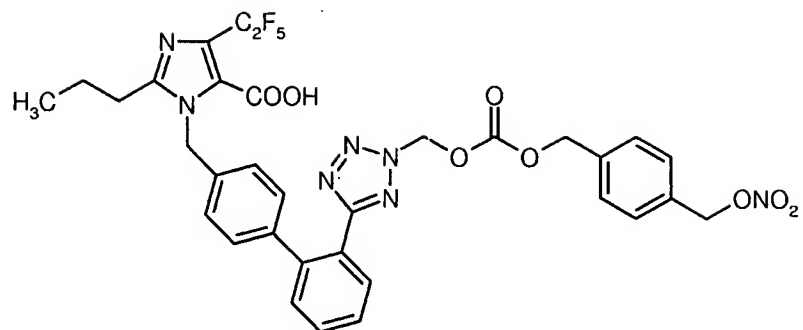
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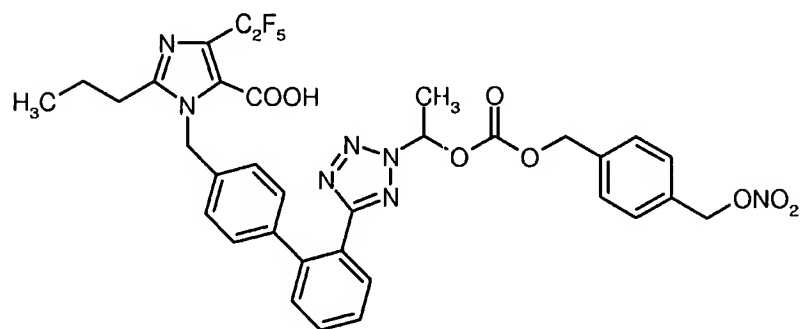
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(331)

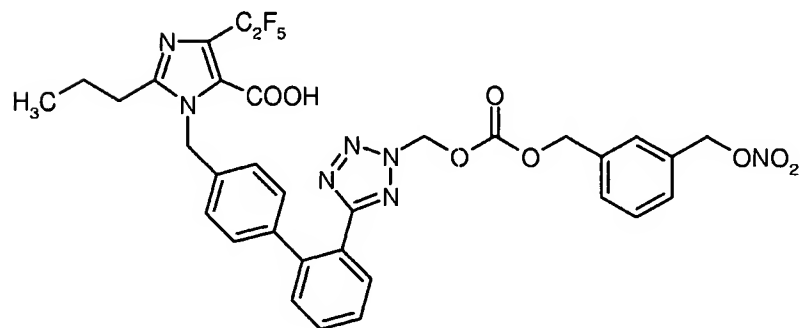


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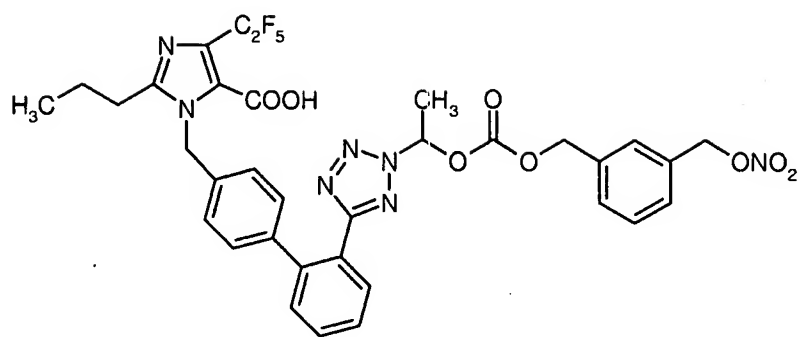


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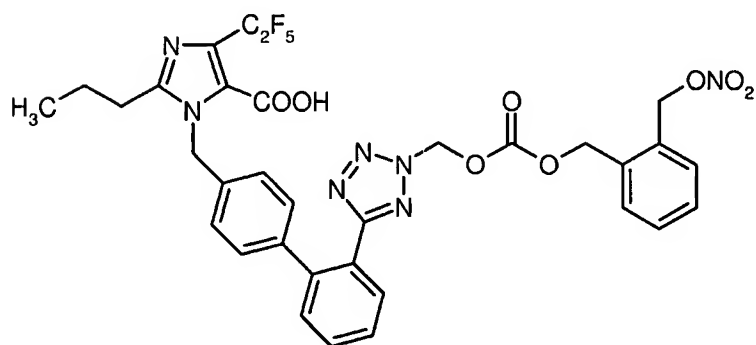
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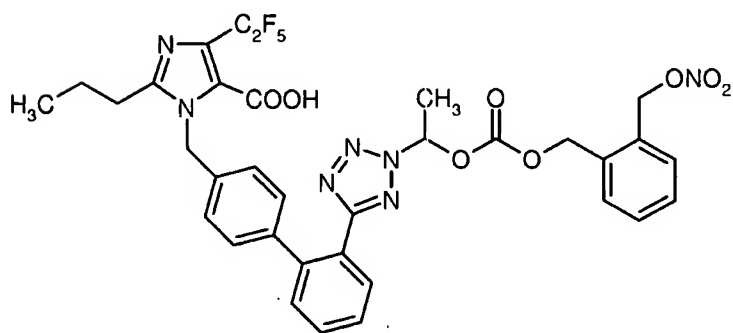
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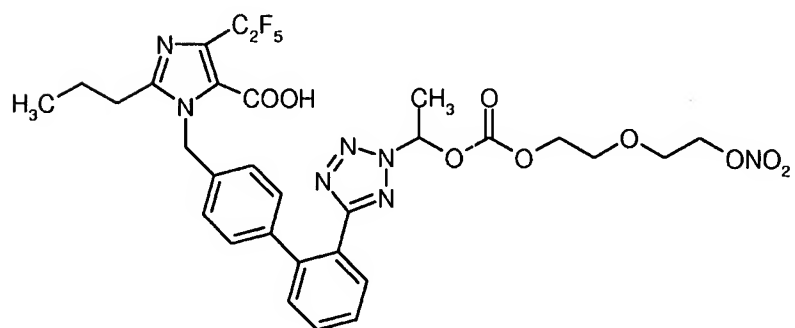
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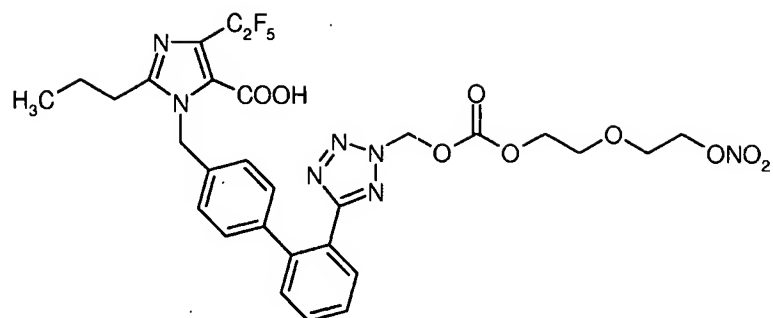
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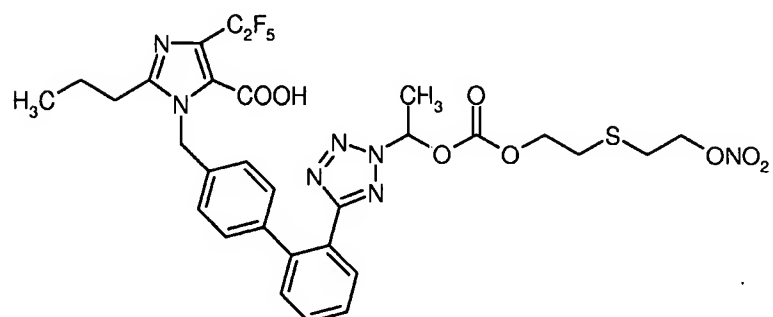
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(338)

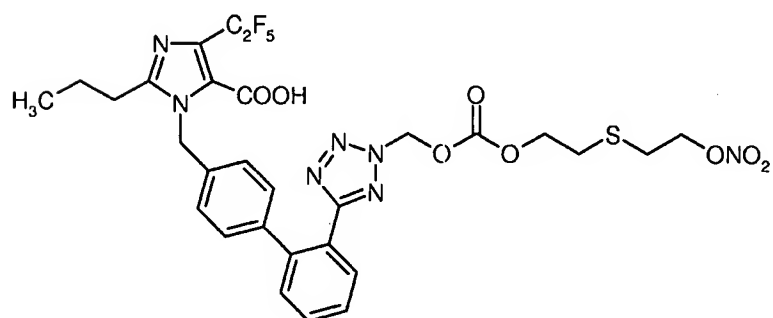


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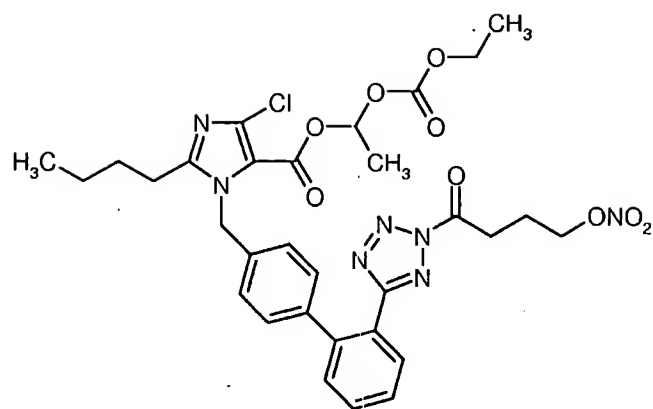


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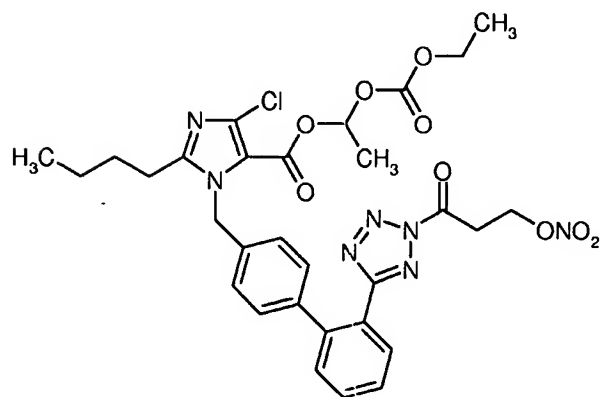
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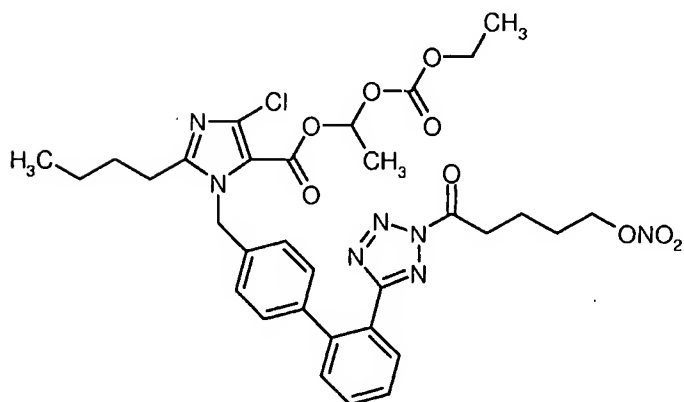
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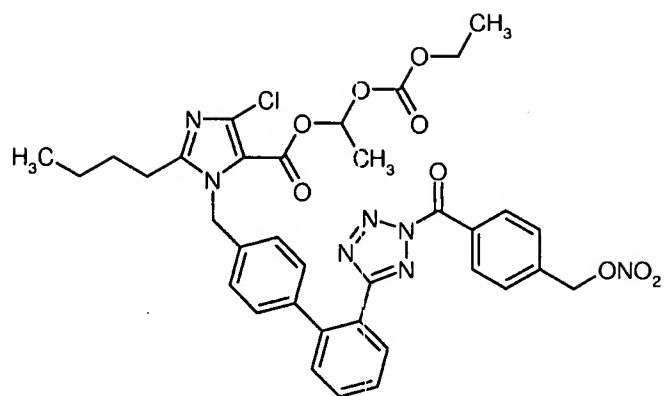
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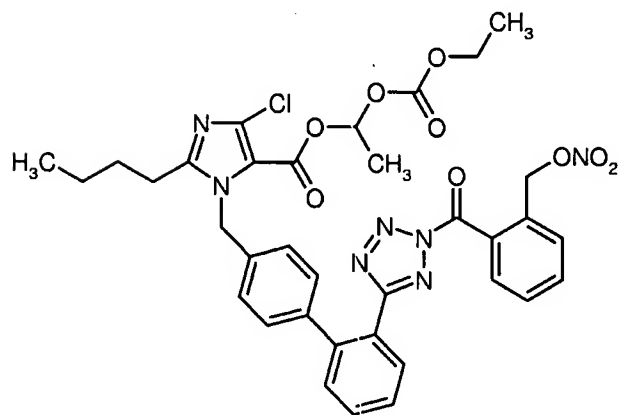
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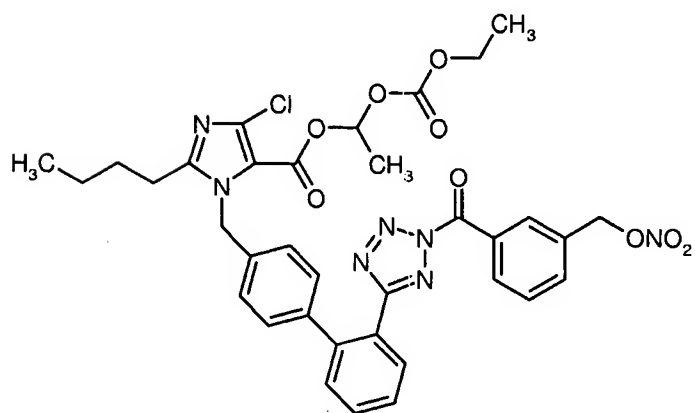
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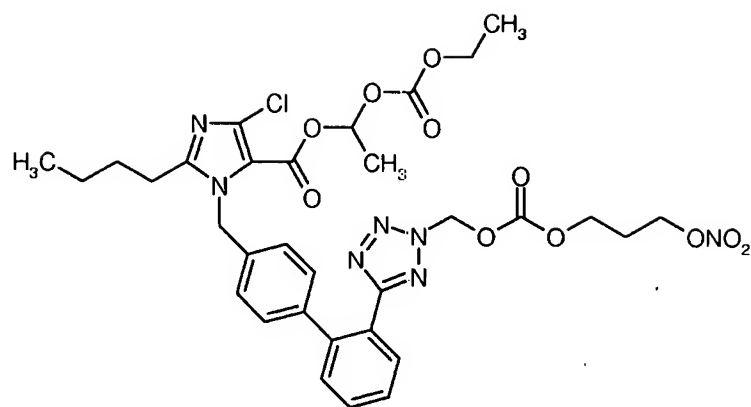
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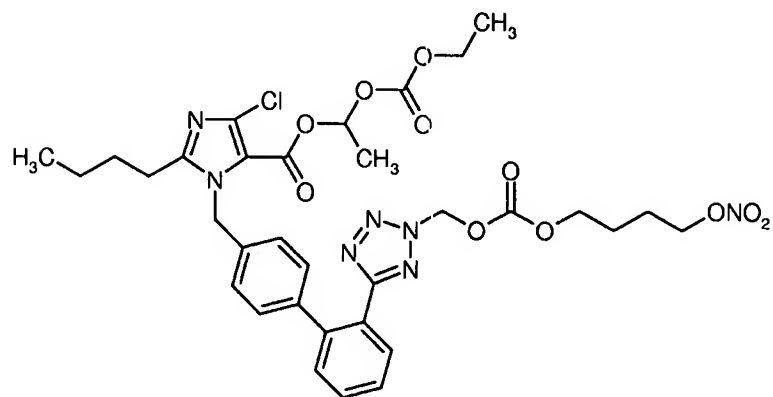
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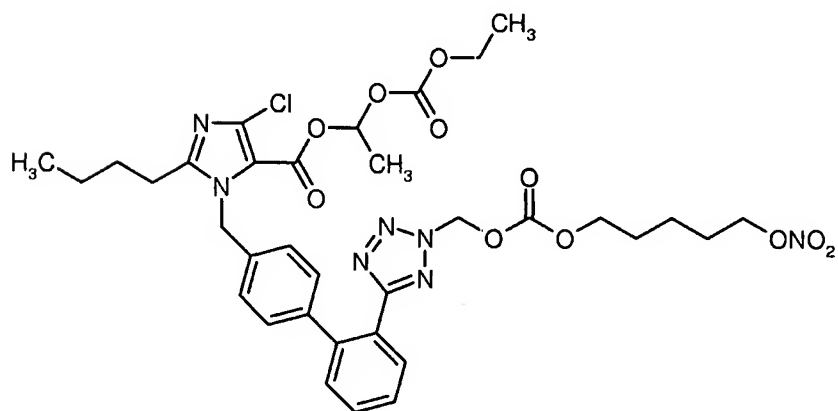
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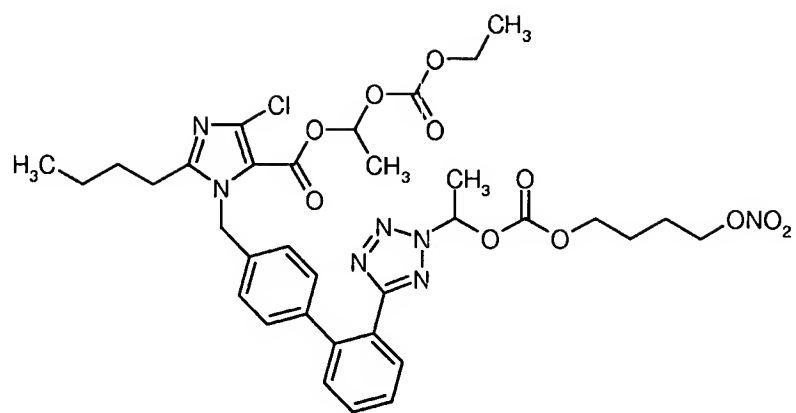
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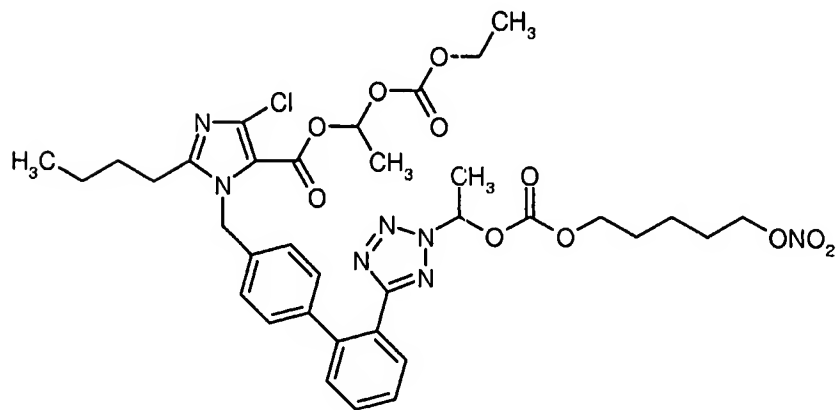
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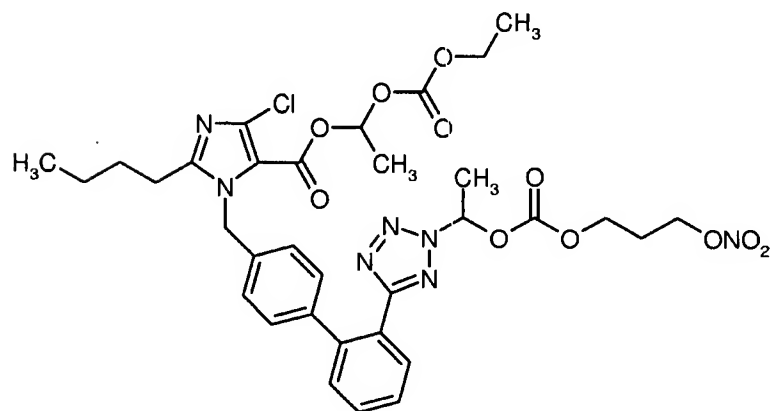
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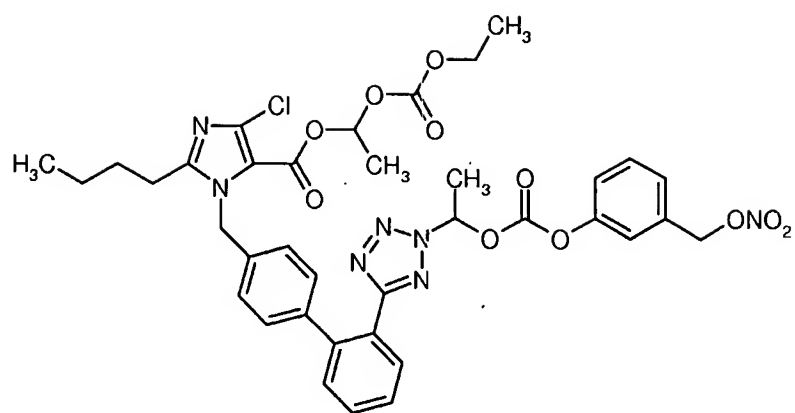
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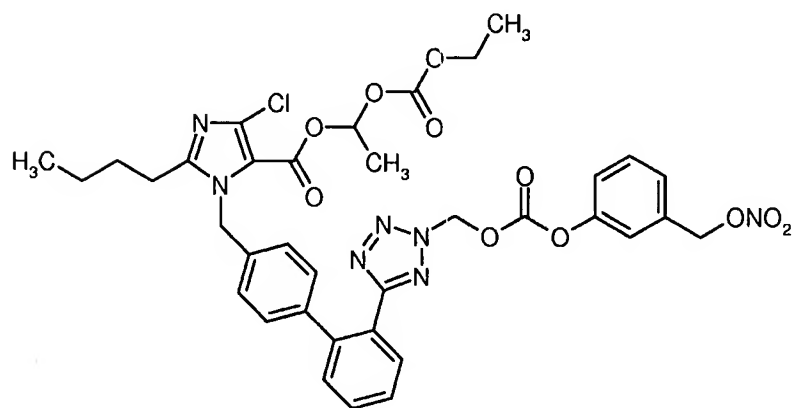
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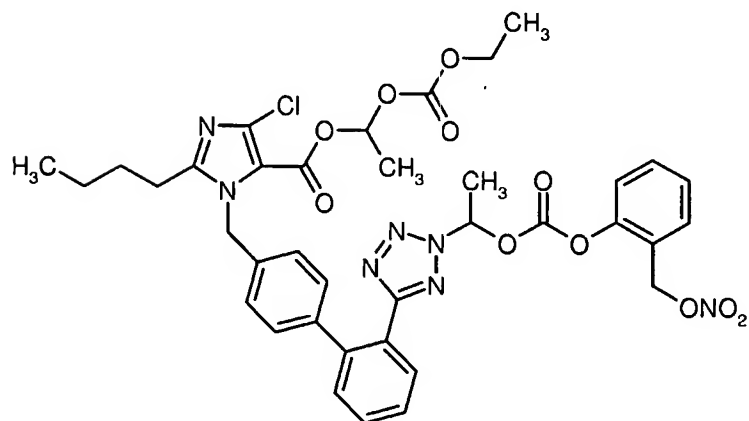
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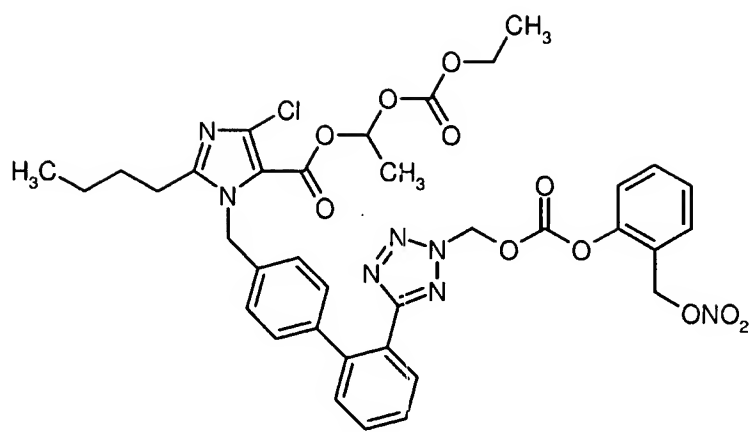
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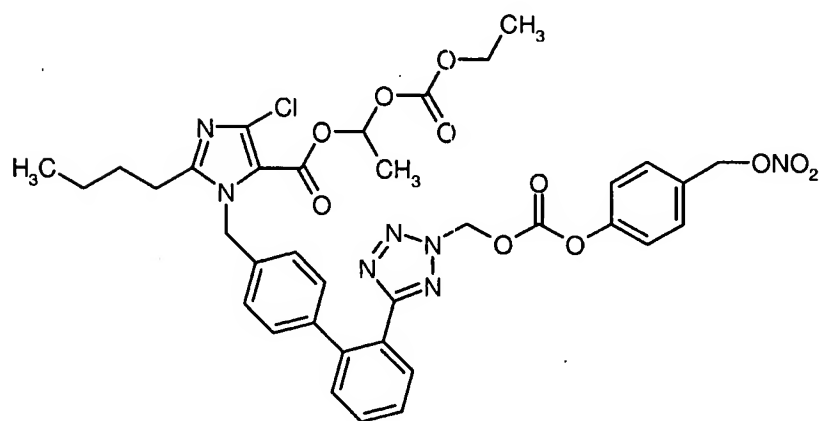
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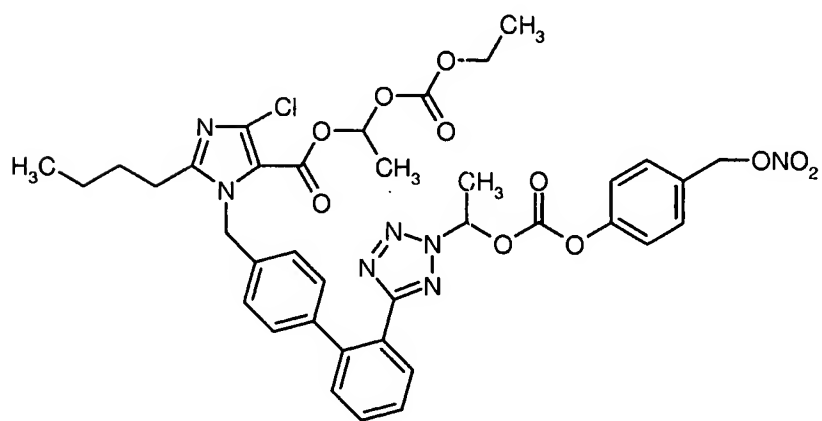
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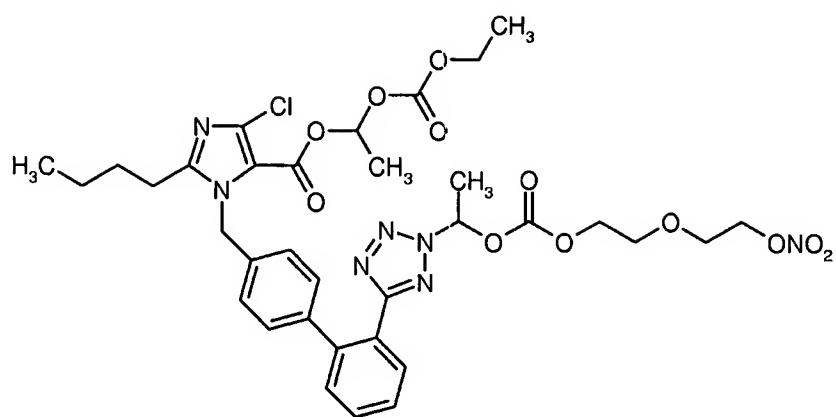
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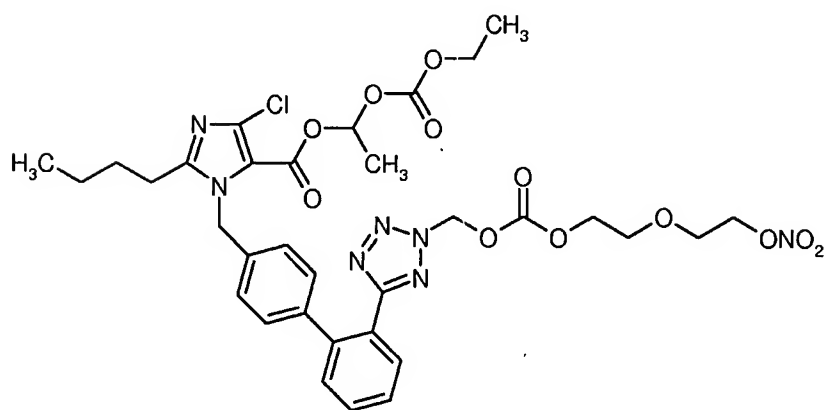
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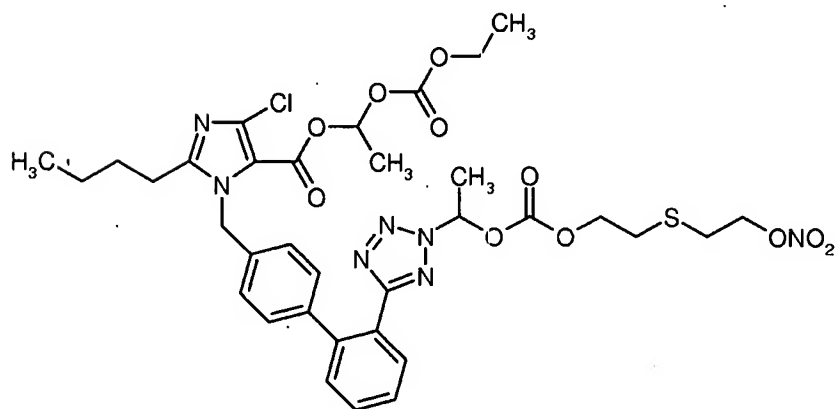
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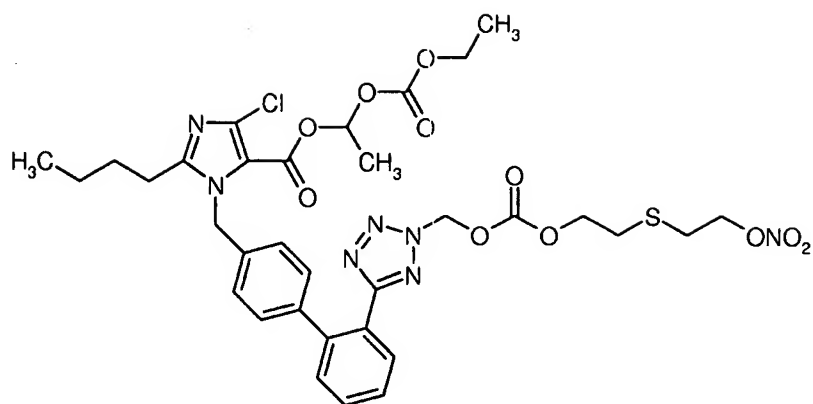
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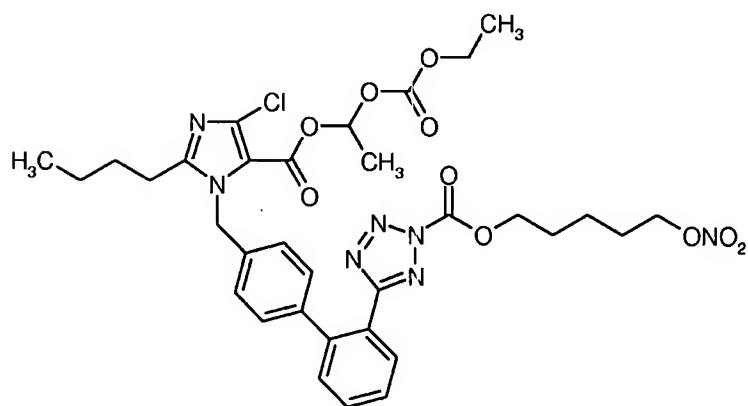
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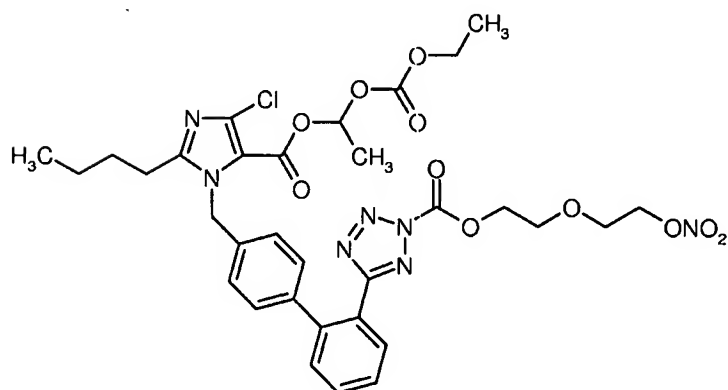
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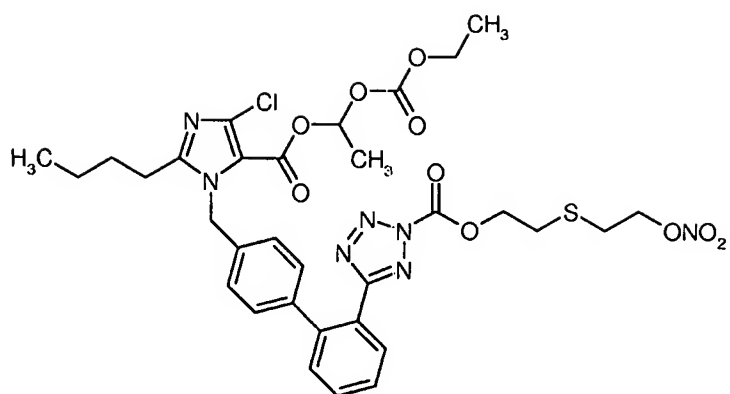
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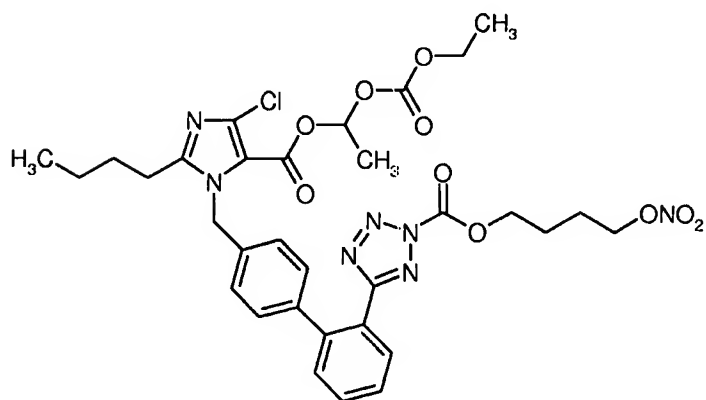
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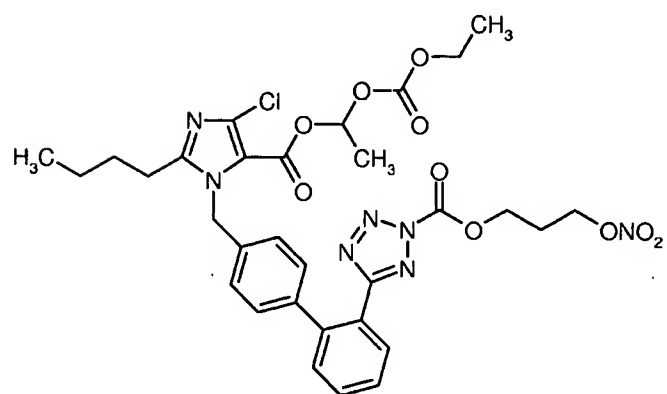
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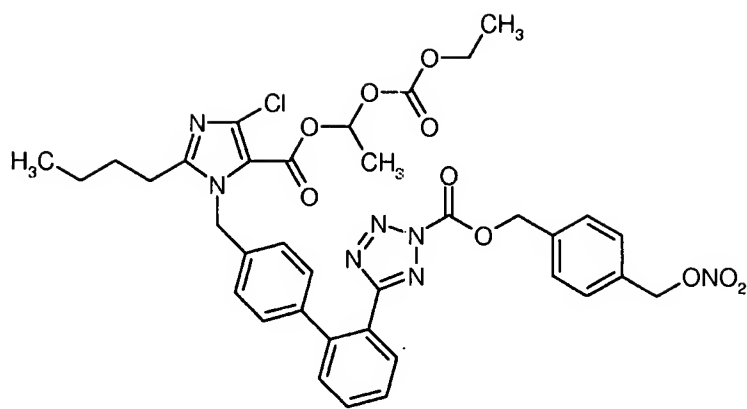
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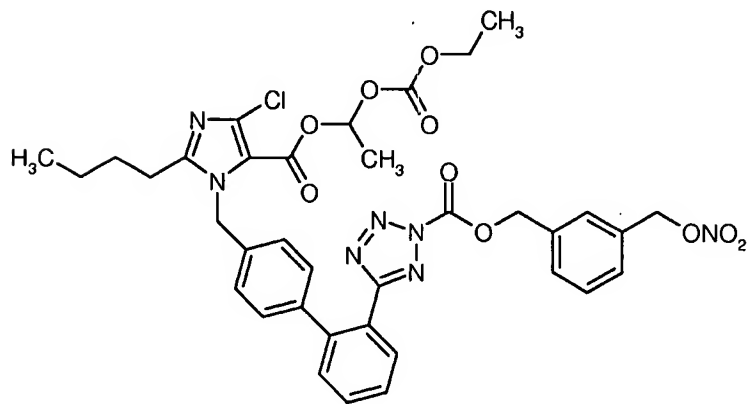
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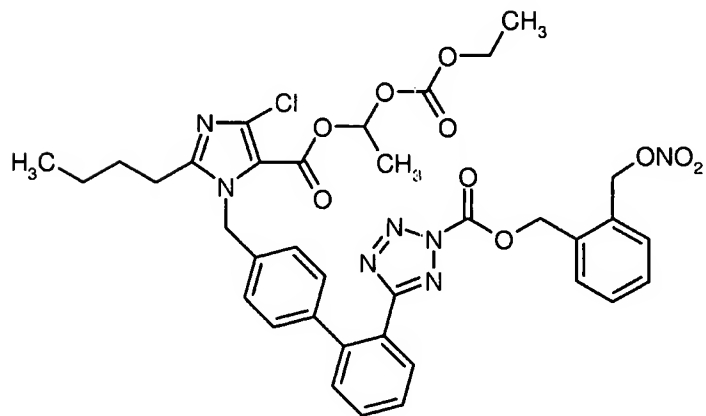
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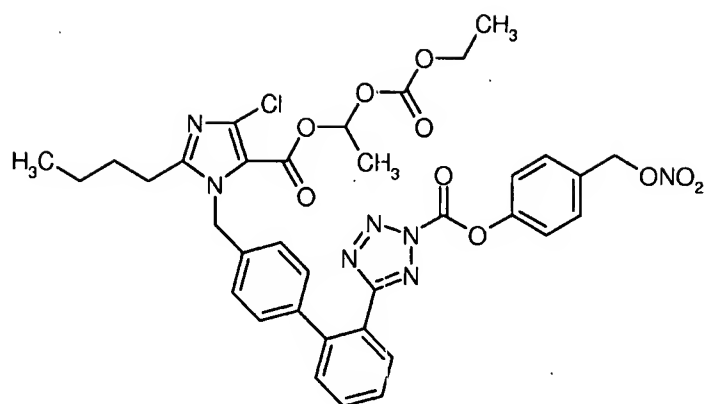
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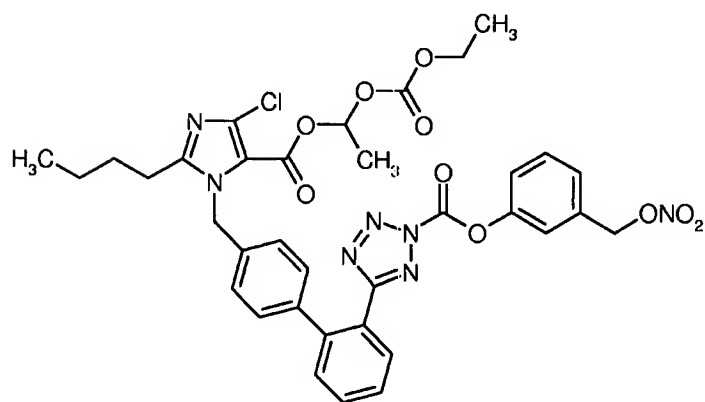
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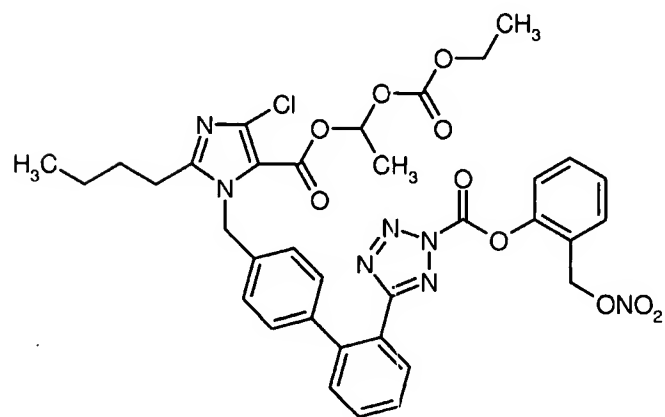
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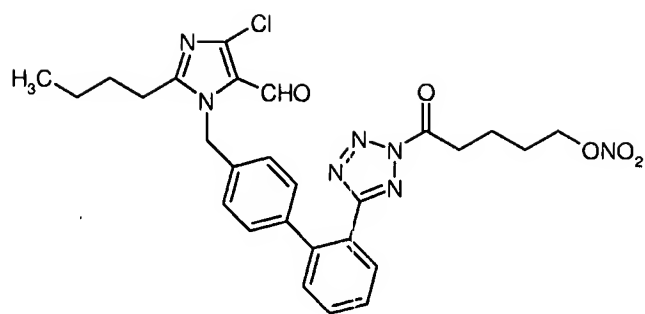
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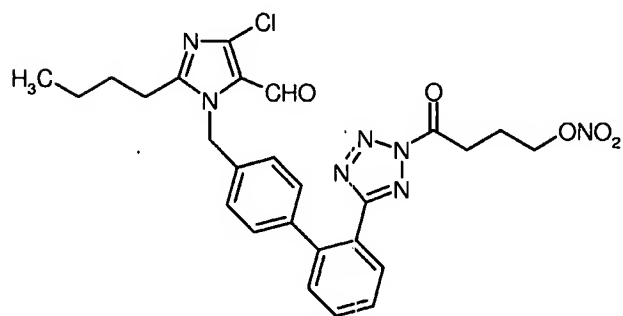
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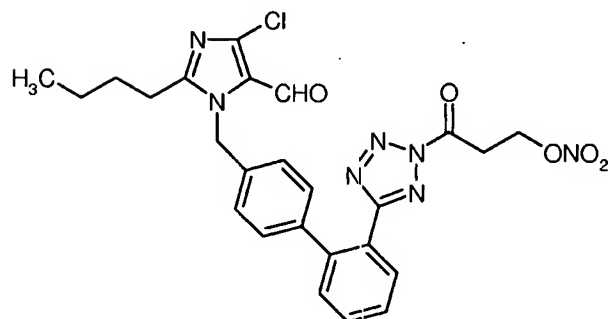
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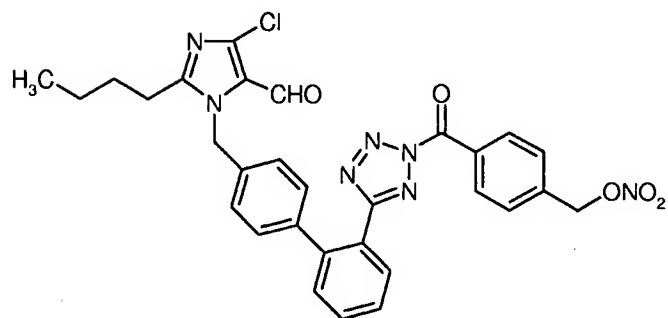
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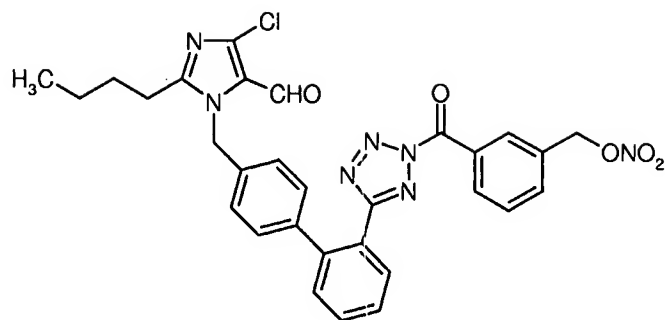
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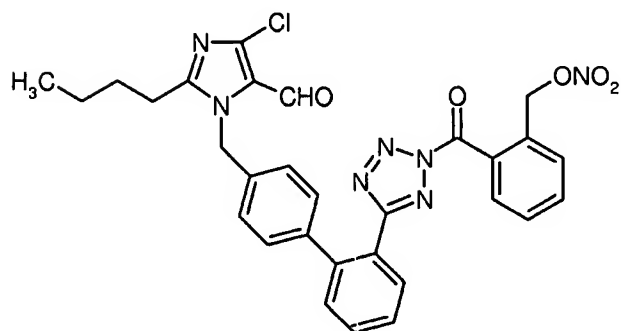
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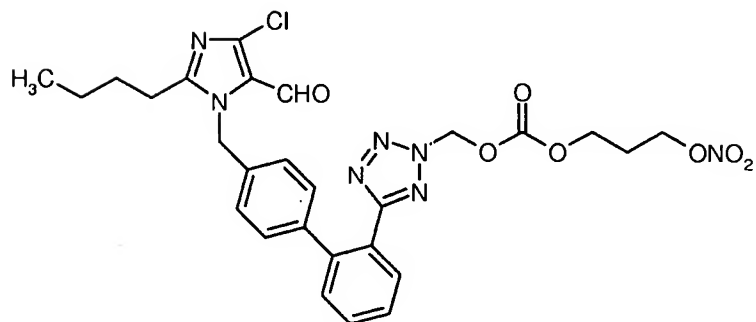
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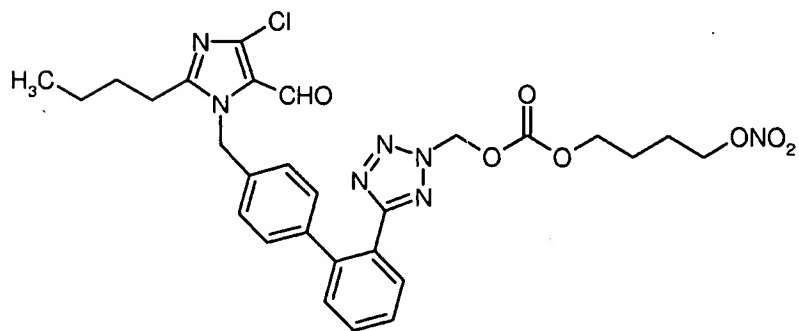
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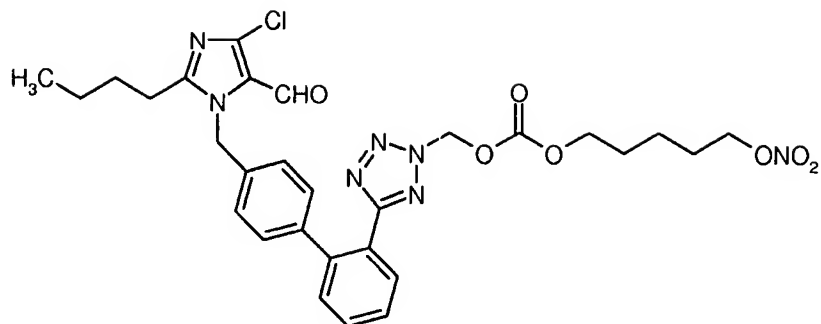
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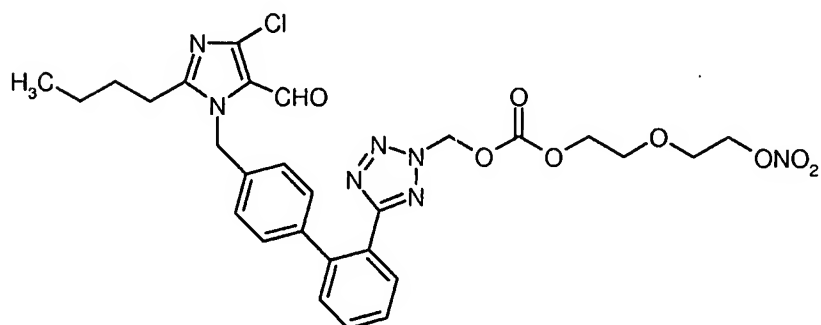
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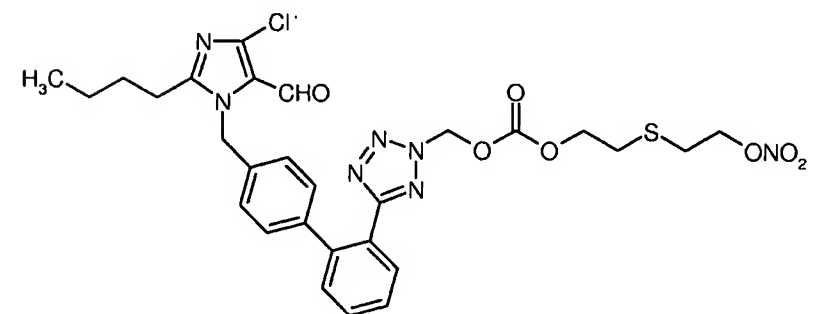
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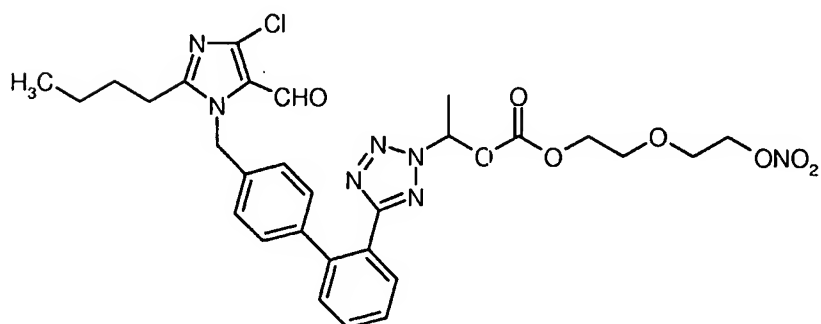
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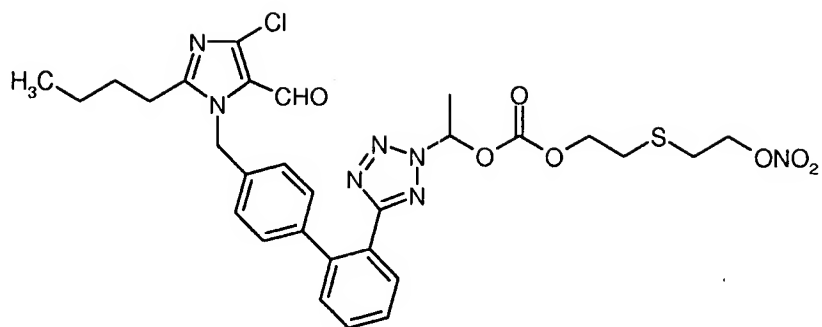
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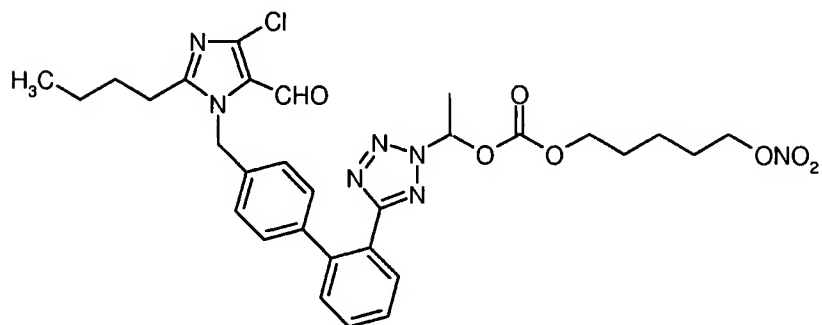
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(392)

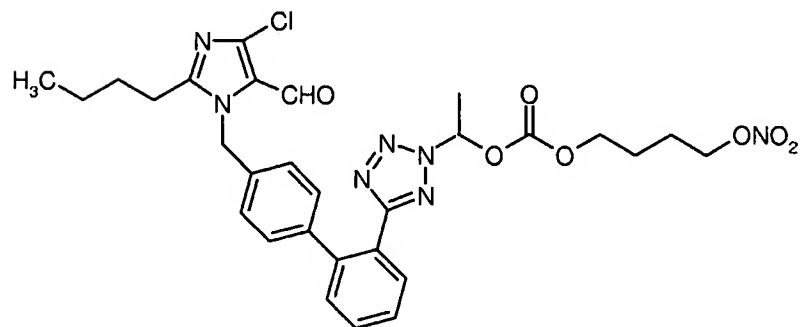


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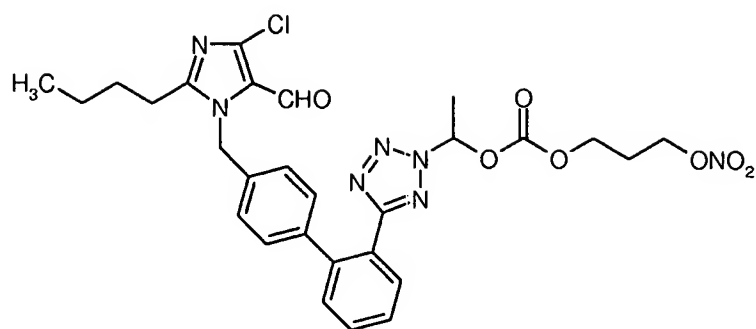


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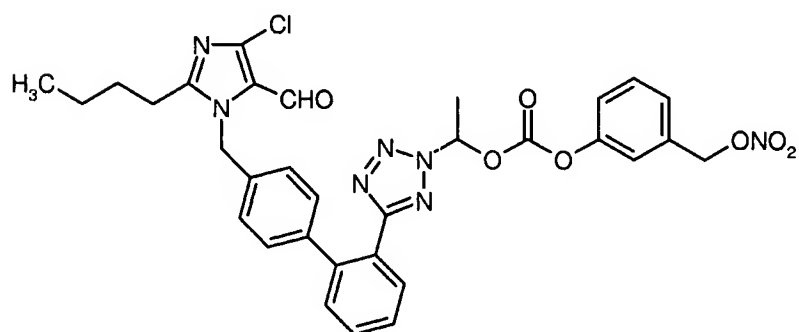
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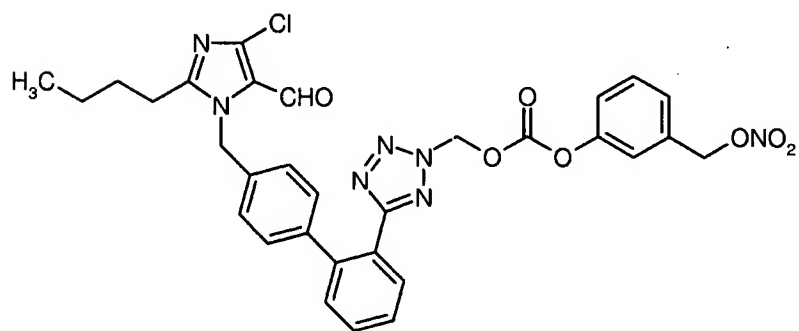
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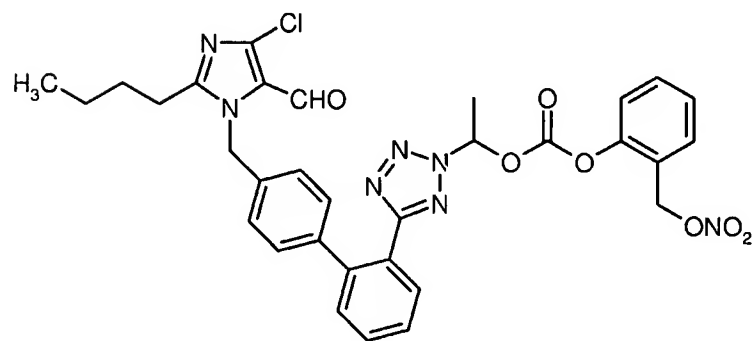
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(397)

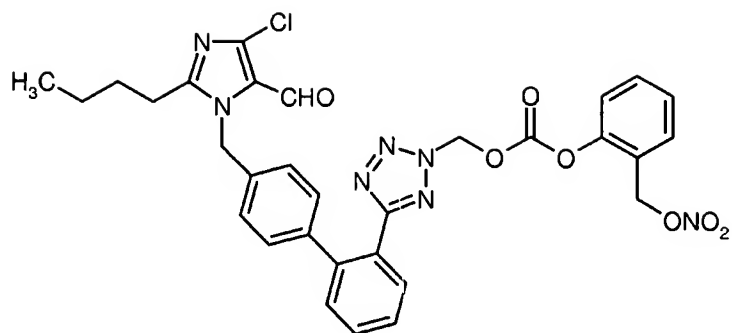


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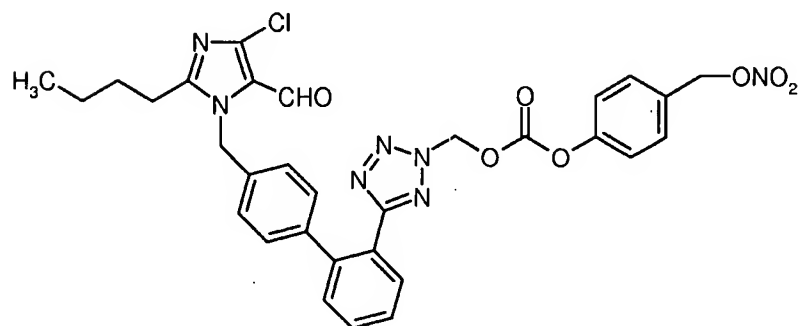


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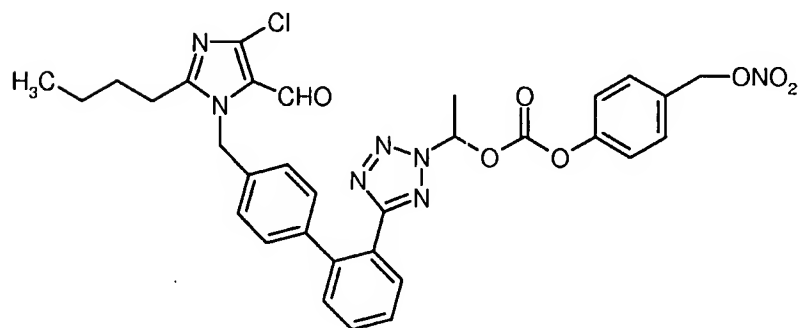
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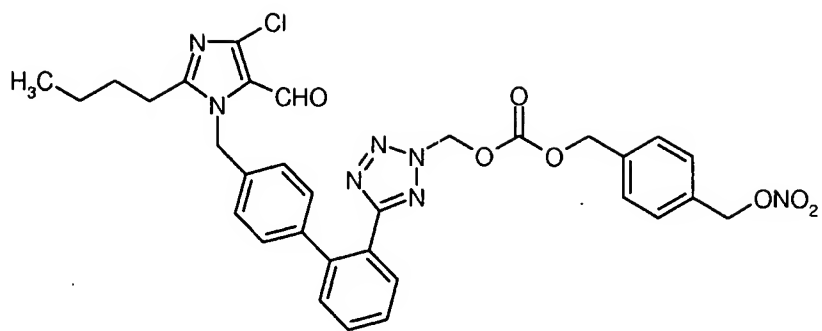
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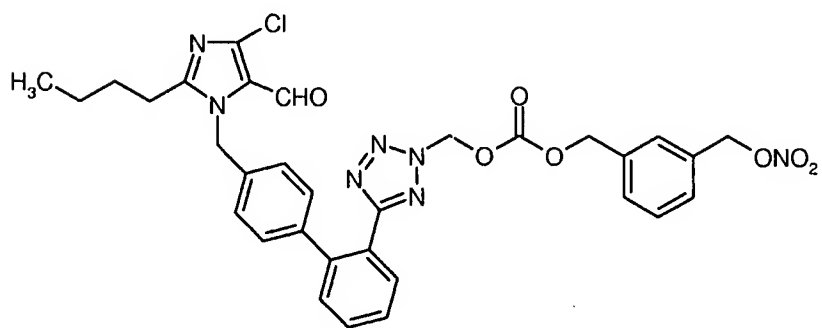
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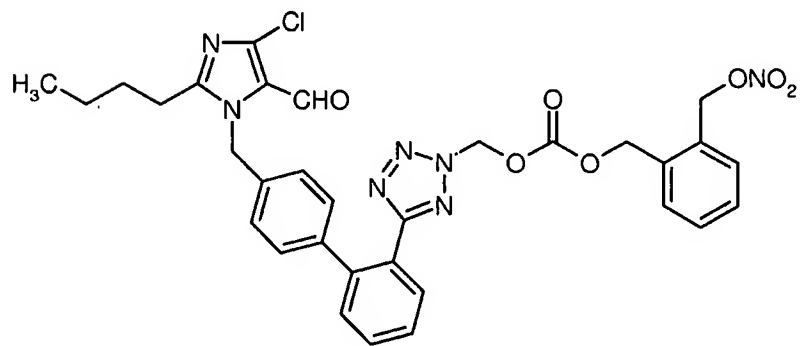
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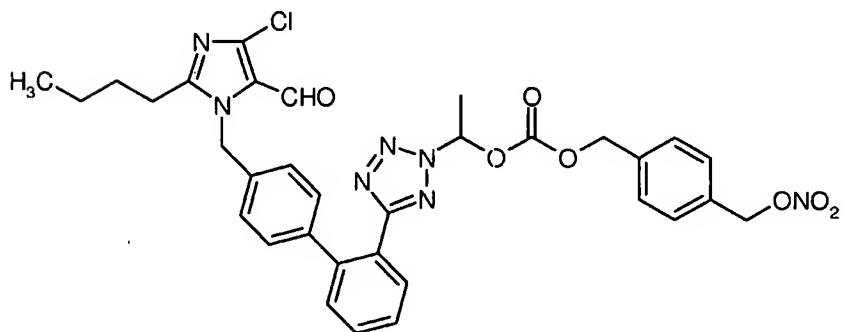
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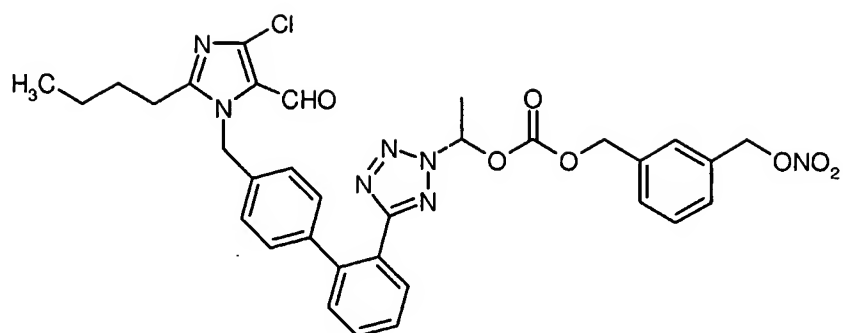
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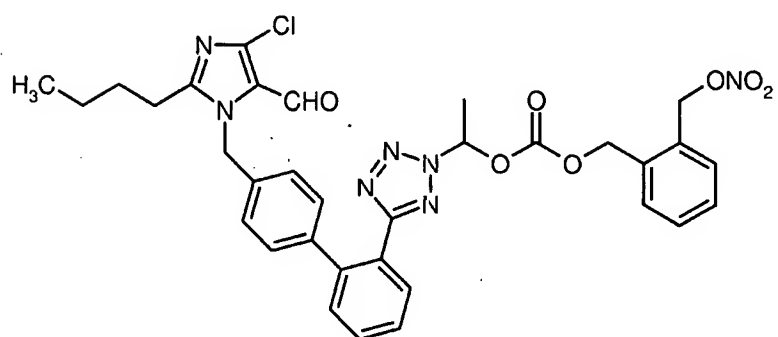
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(406)

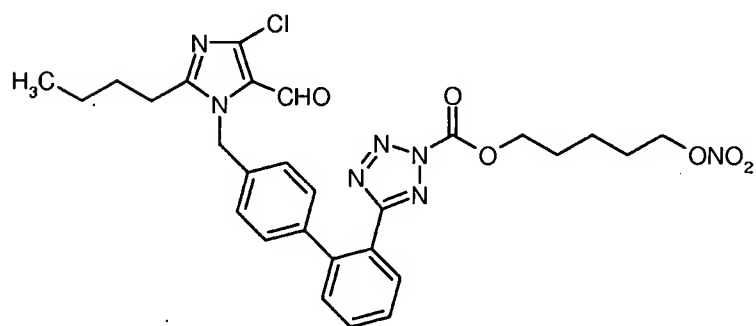


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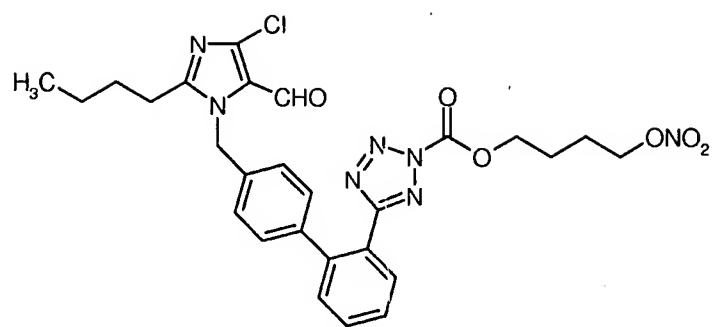


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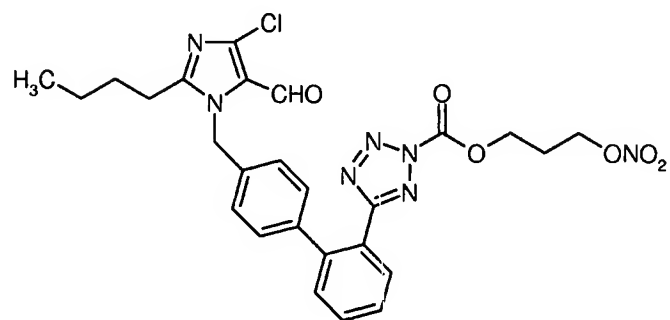
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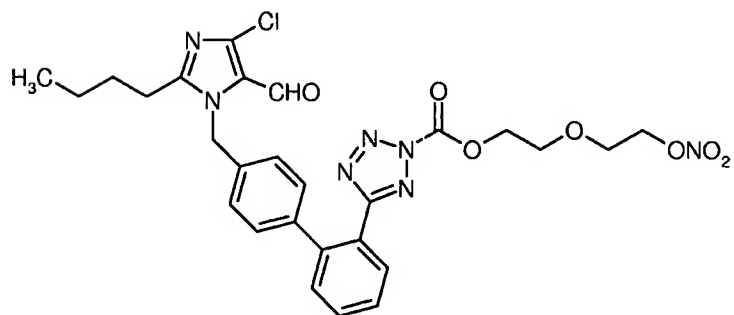
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(410)

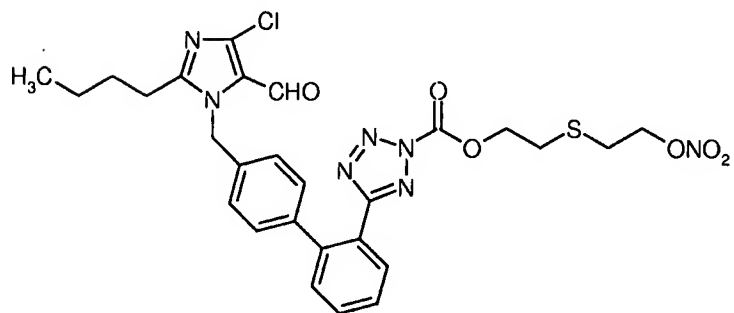


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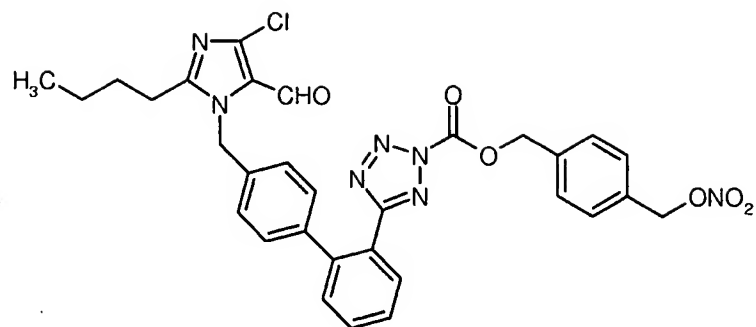


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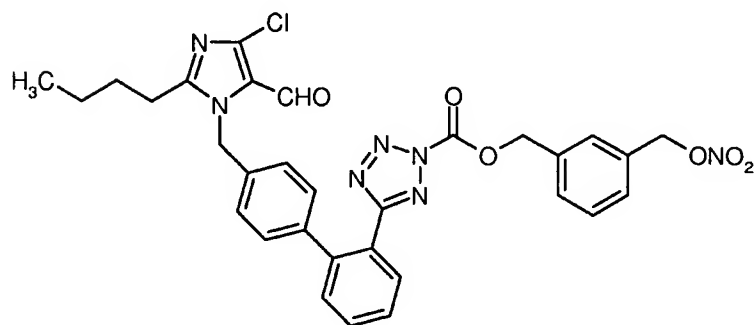
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(413)

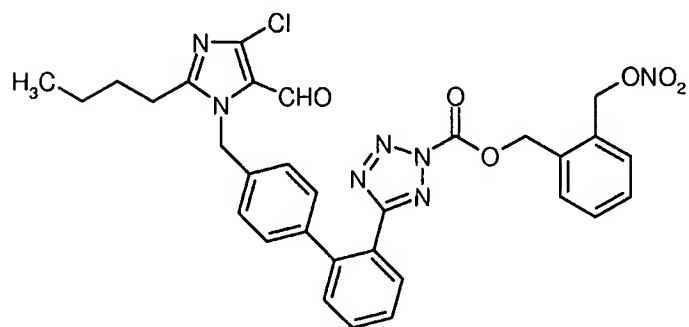


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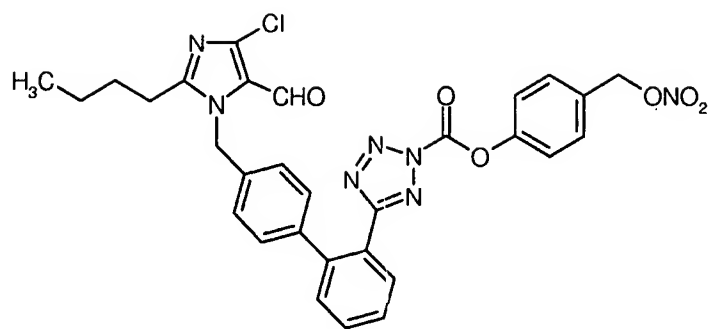


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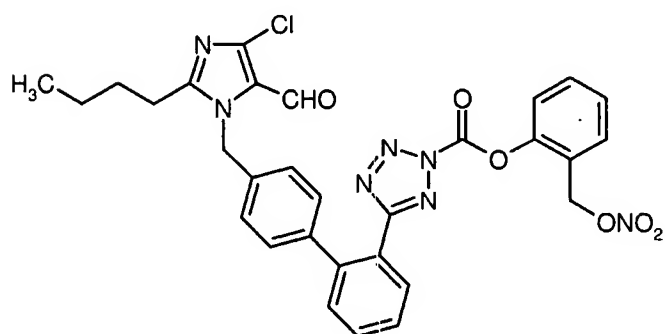
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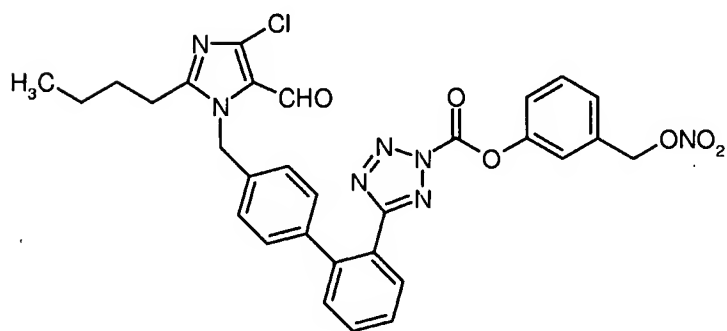
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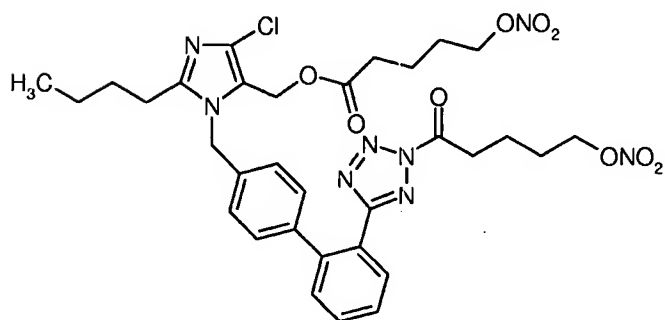
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(418)

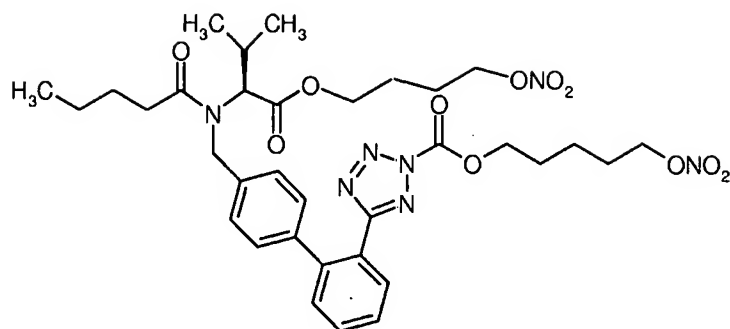


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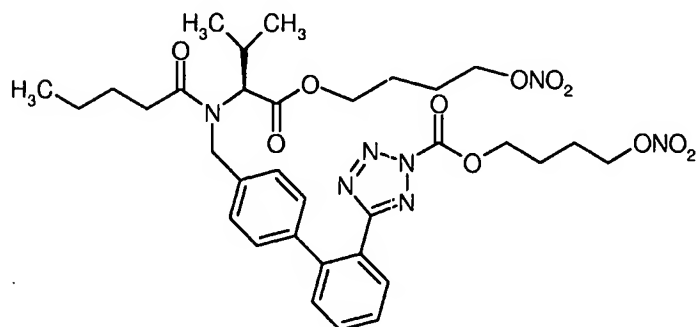


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(420)

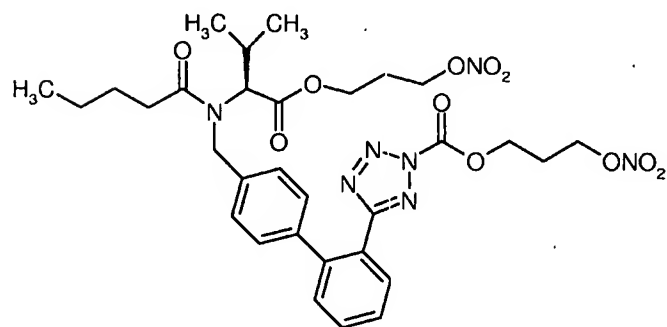


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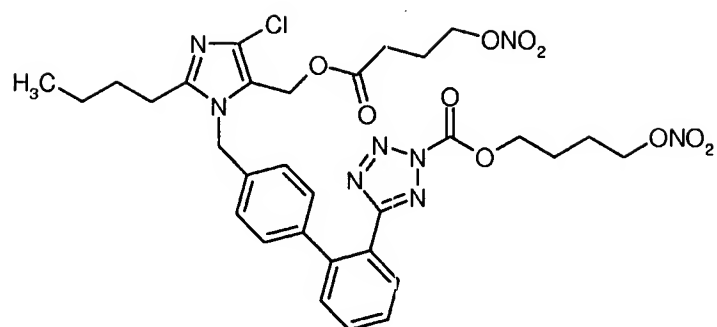
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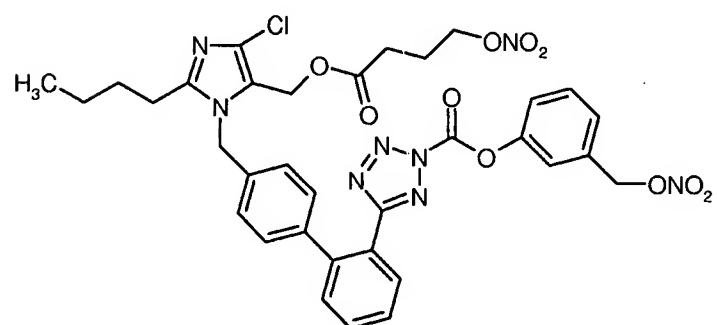


(423)

(427)

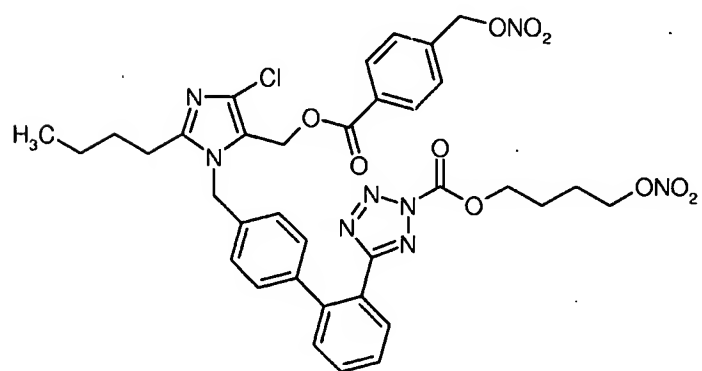


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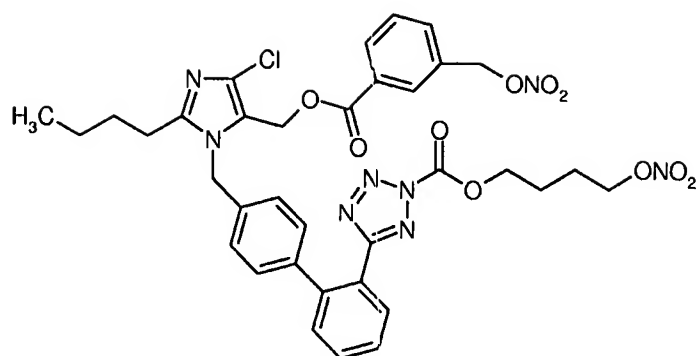


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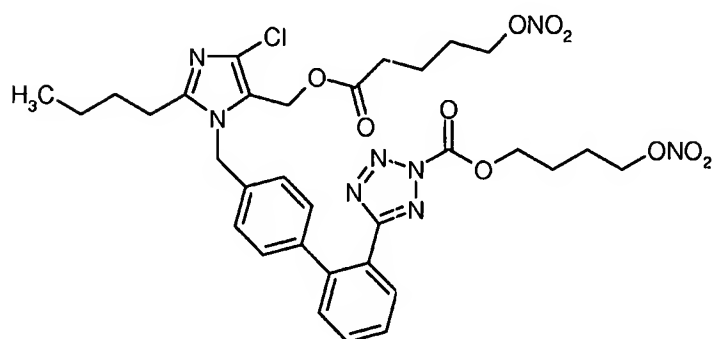
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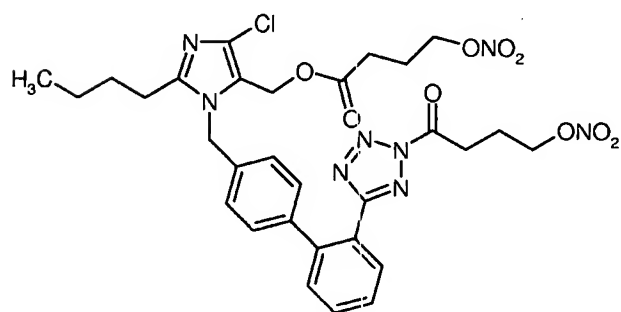
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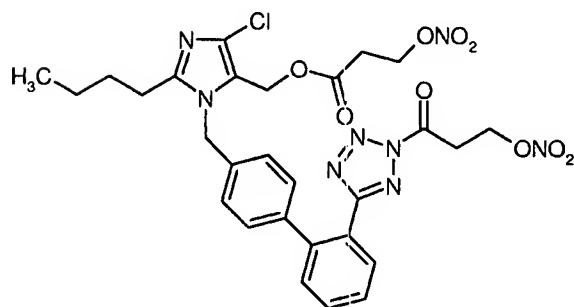
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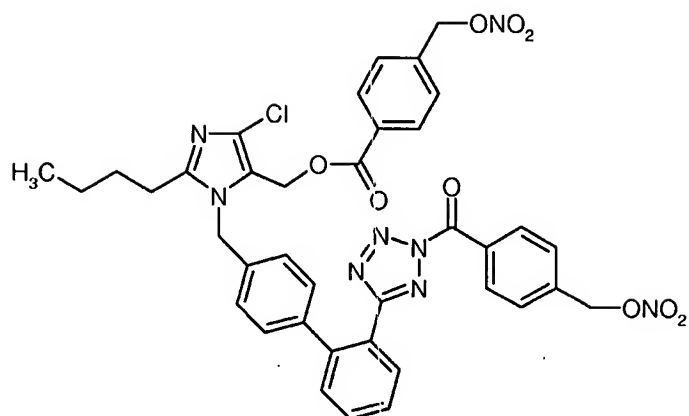
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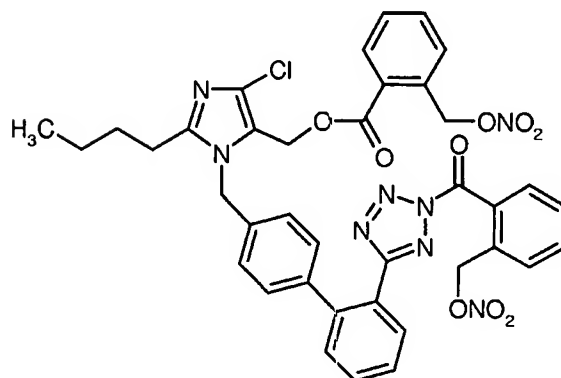
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(434)

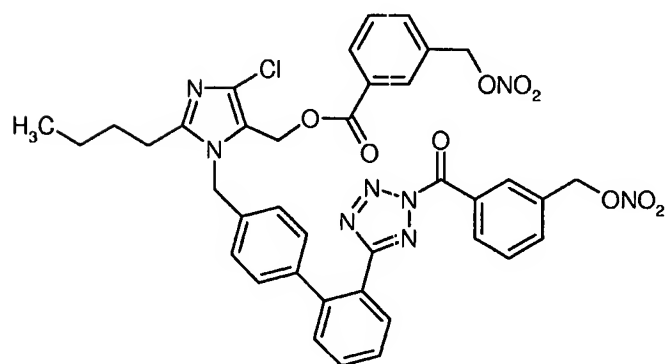


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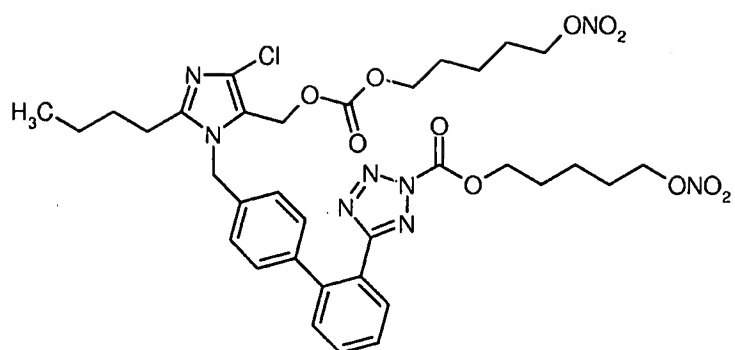


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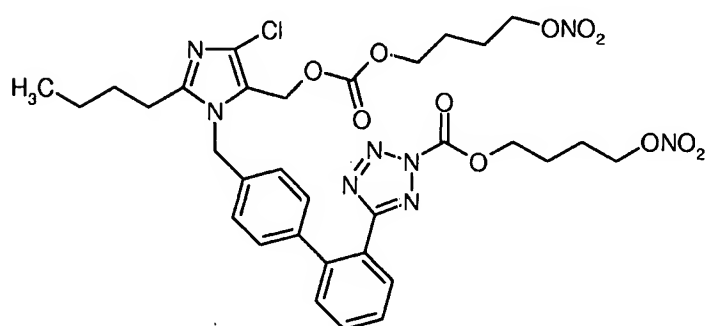
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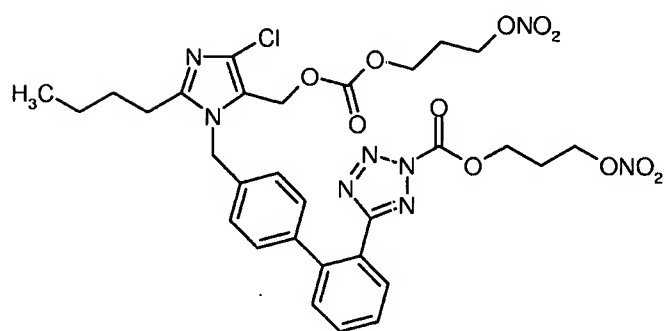
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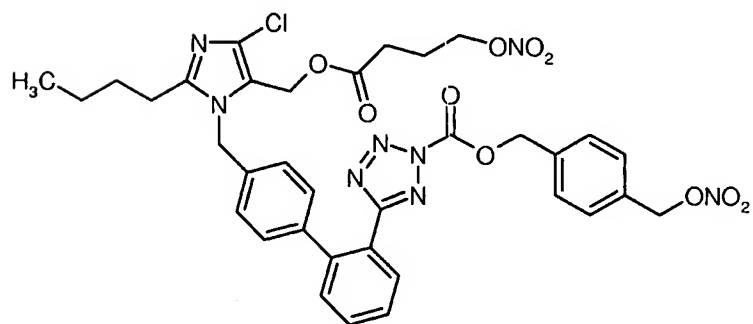
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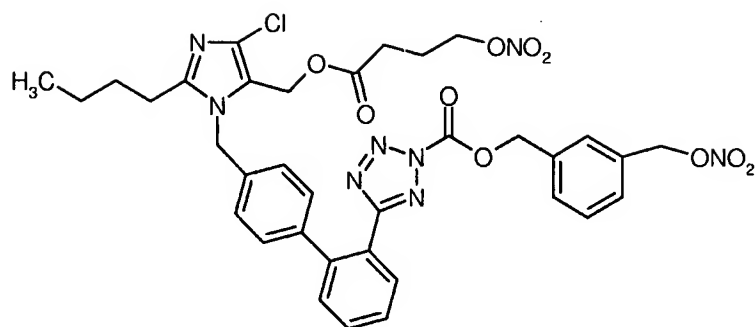
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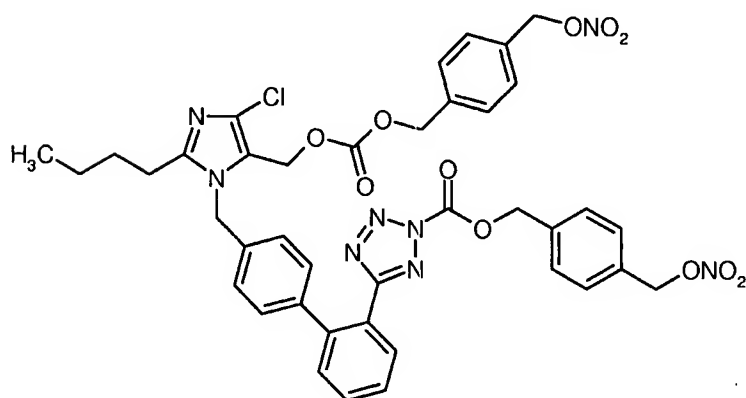
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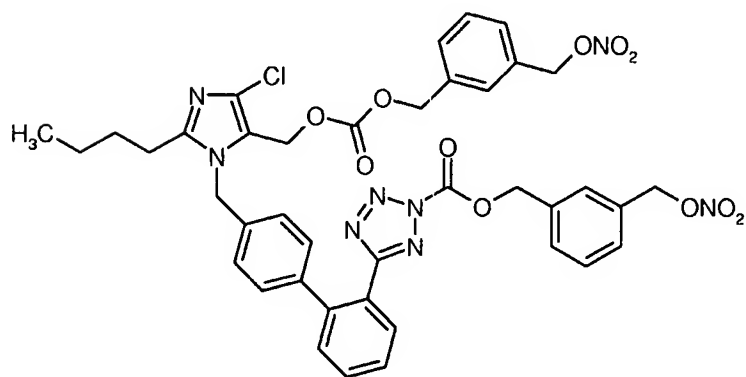
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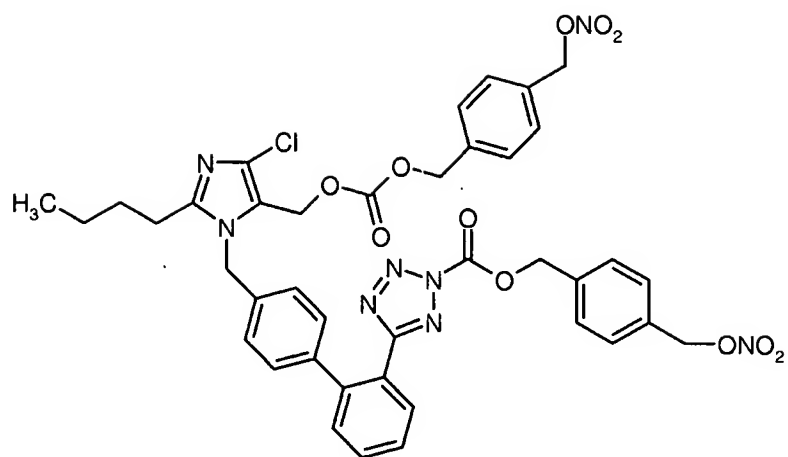
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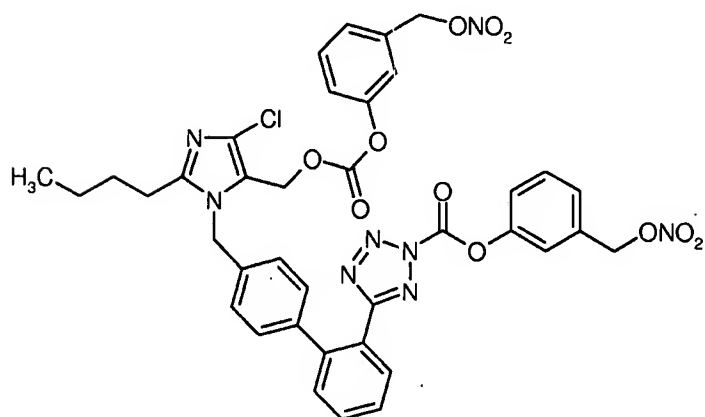
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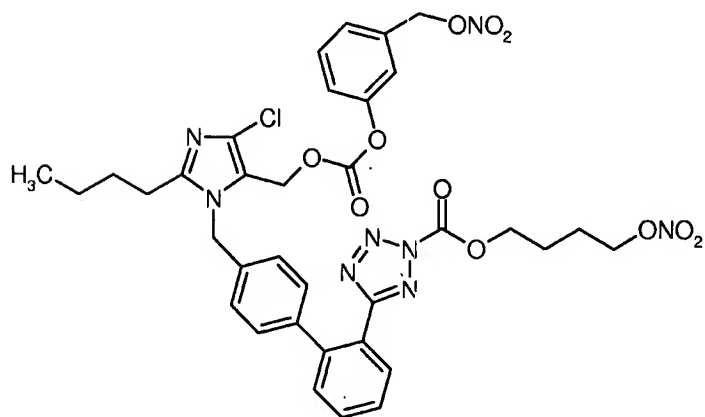
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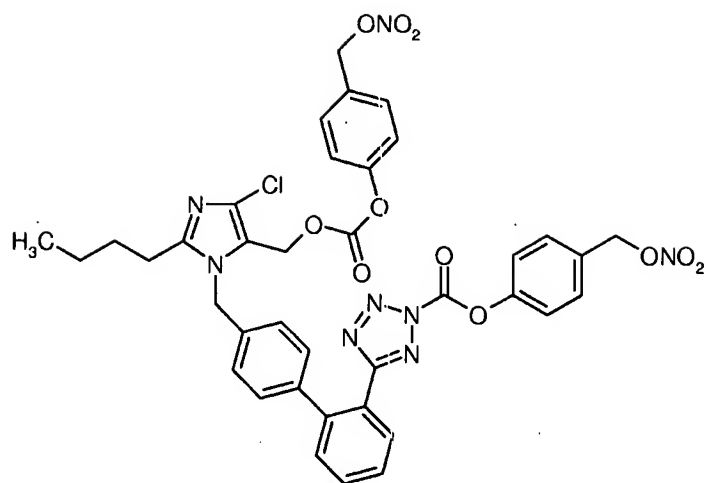
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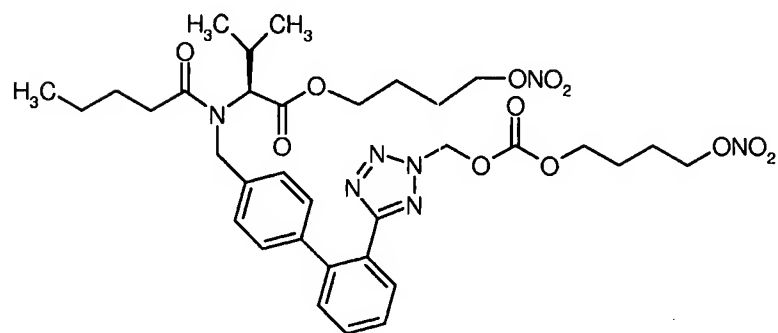
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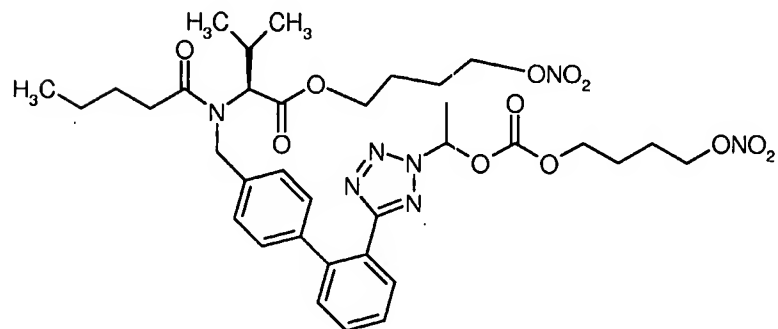
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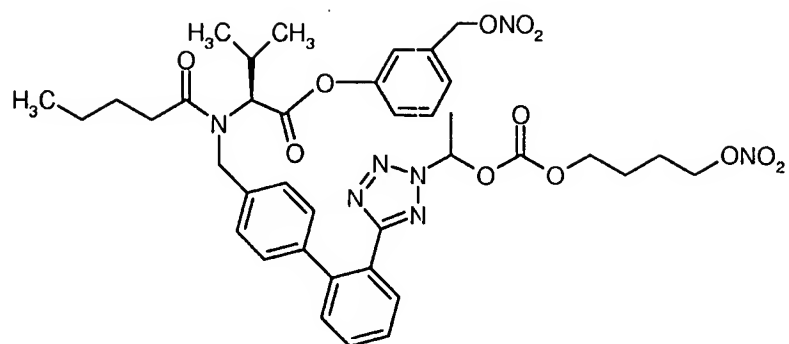
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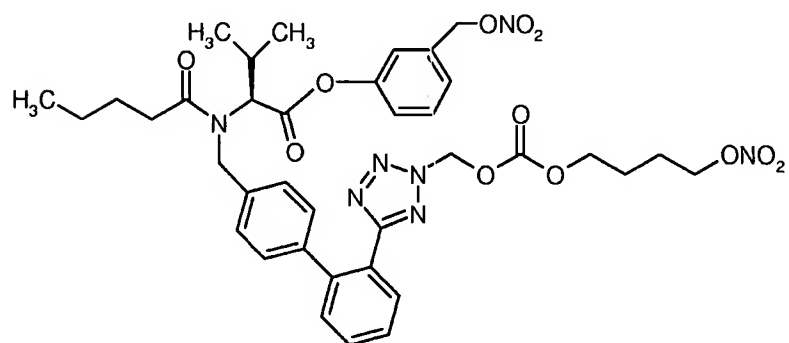
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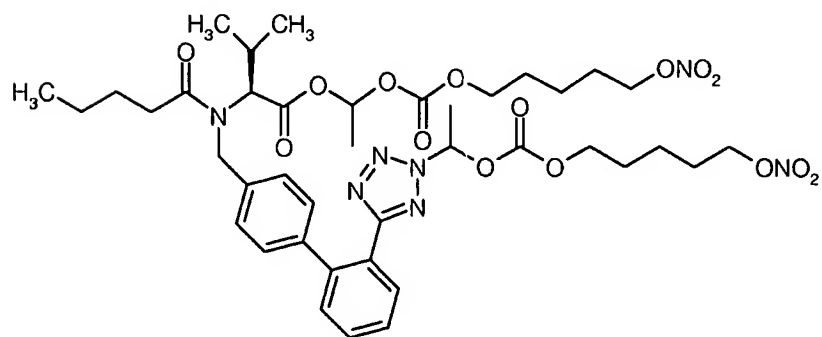
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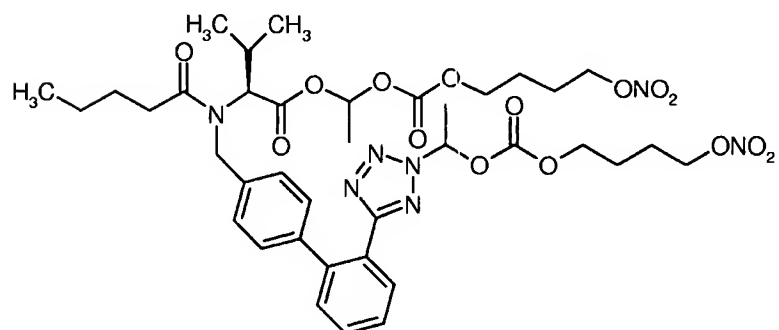
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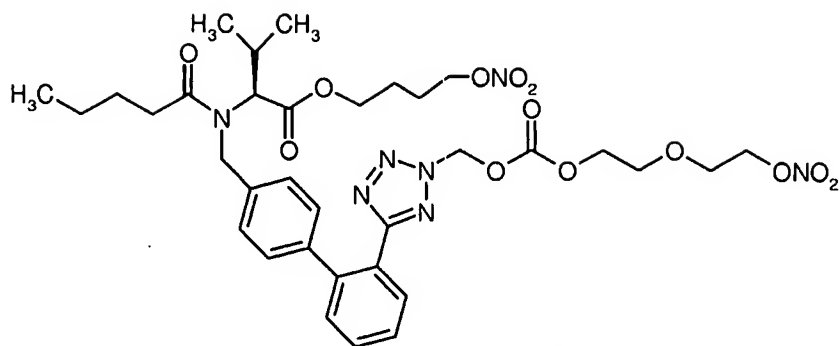
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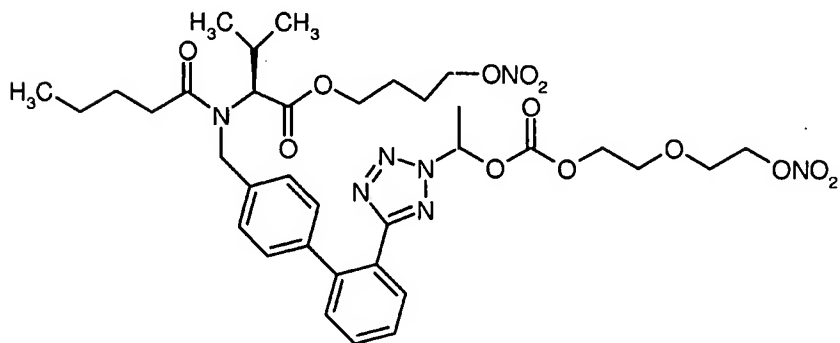
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(454)

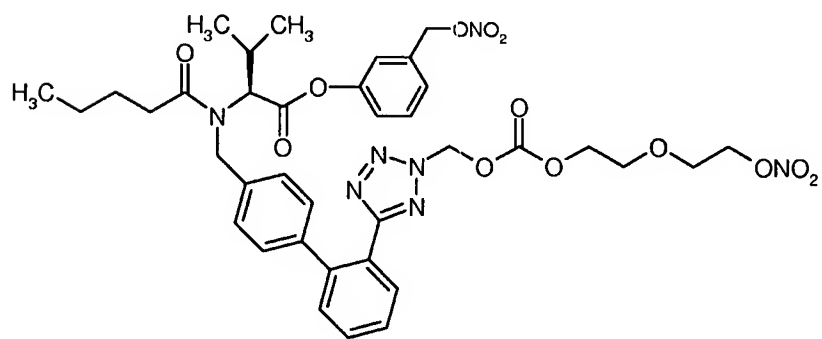


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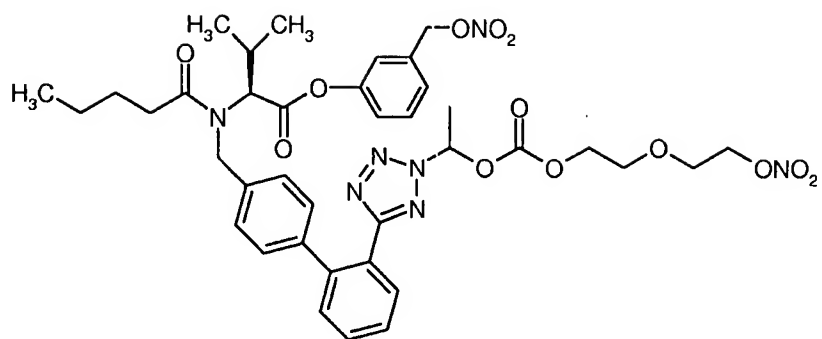


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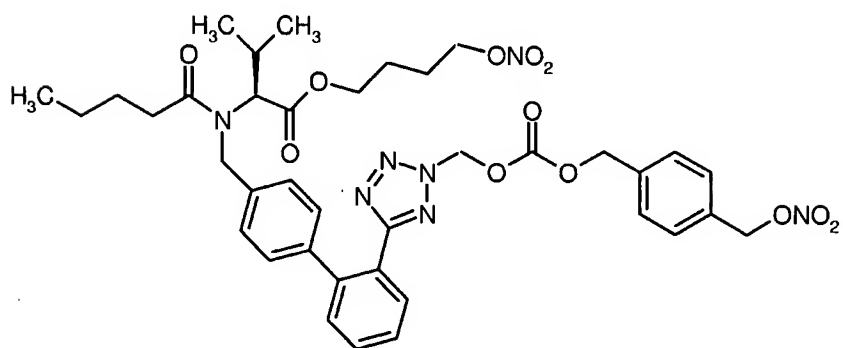
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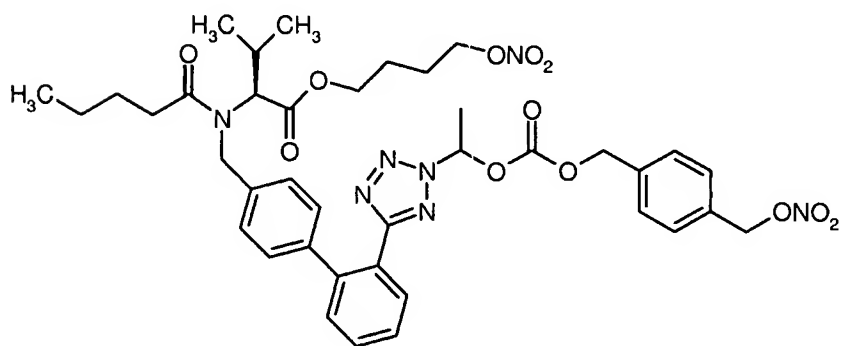
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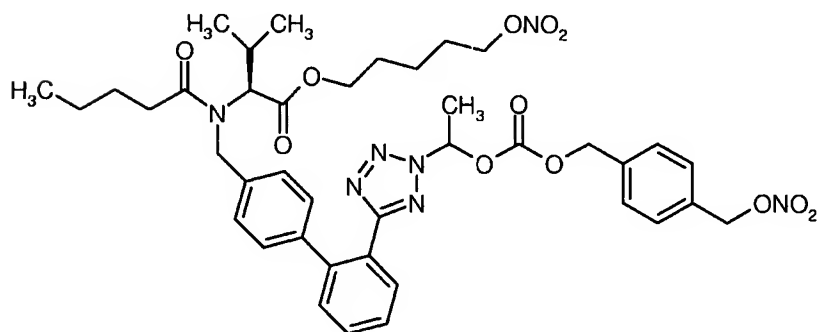
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(459)

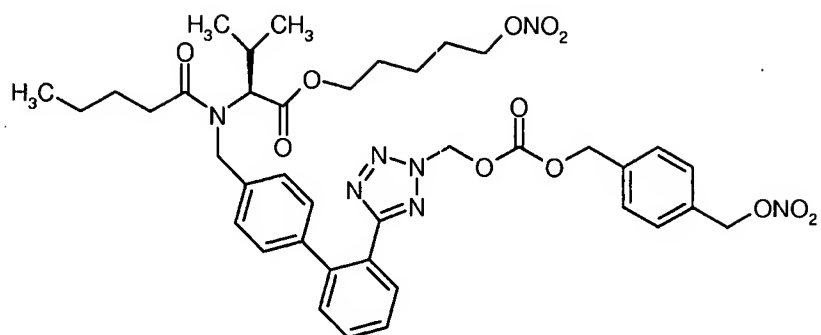


(460)

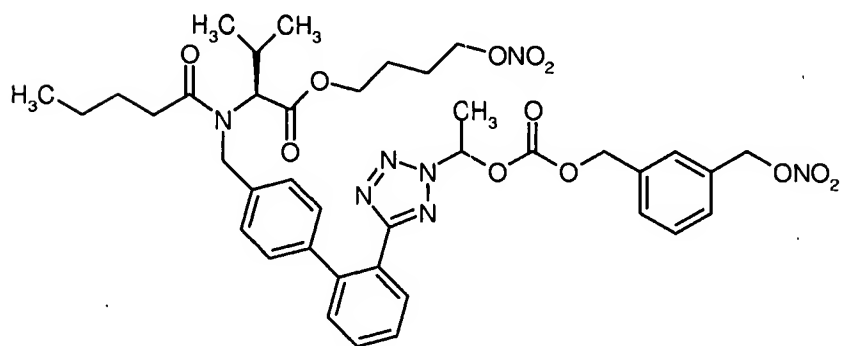


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(461)

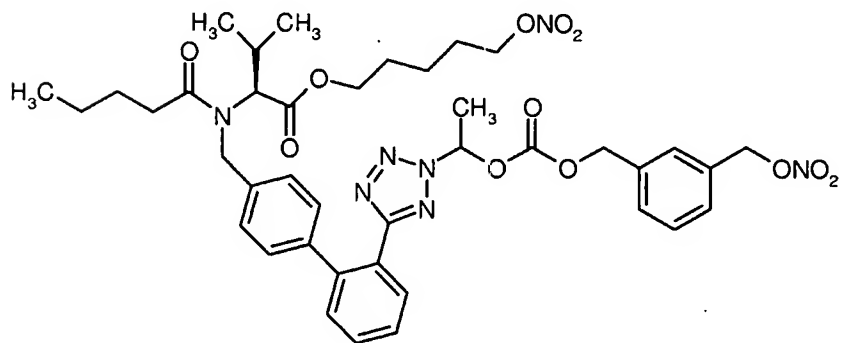


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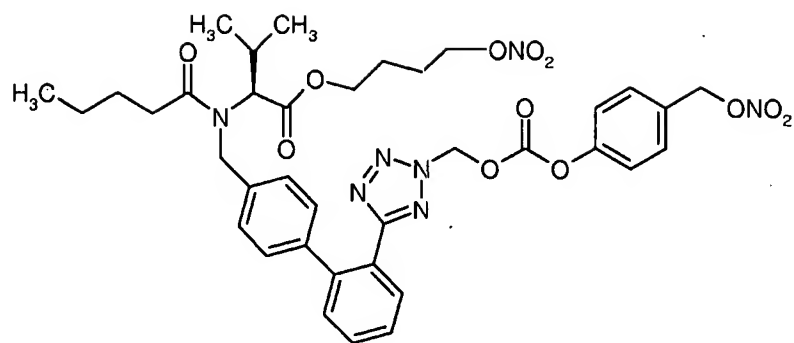


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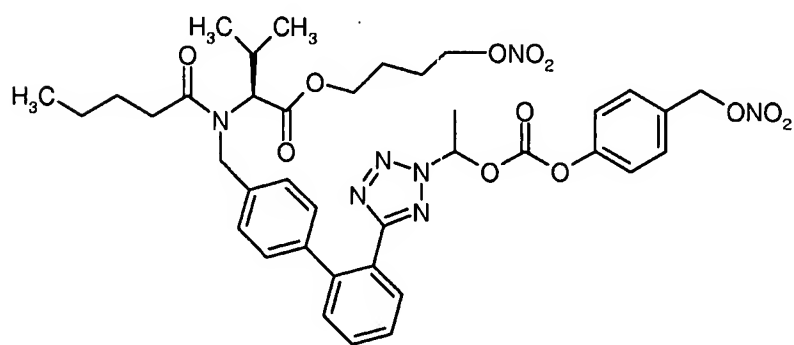
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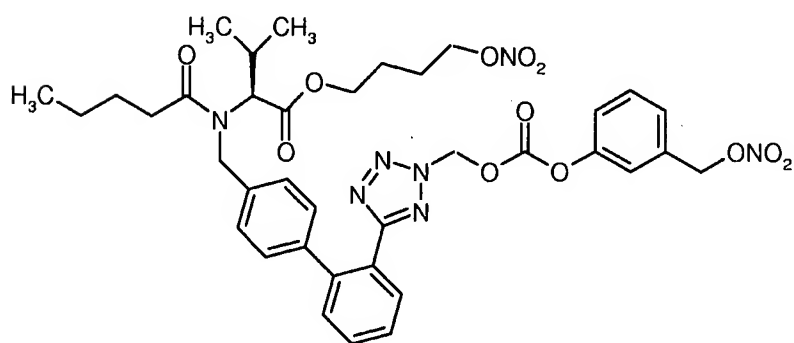
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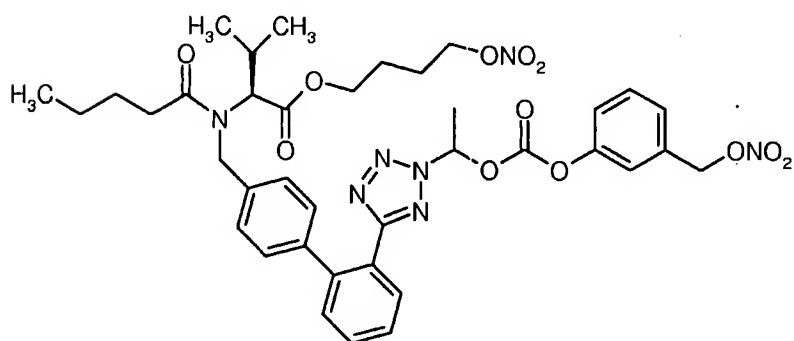
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(466)

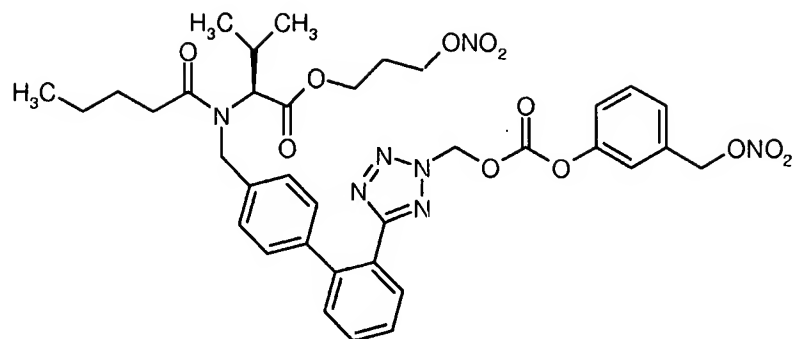


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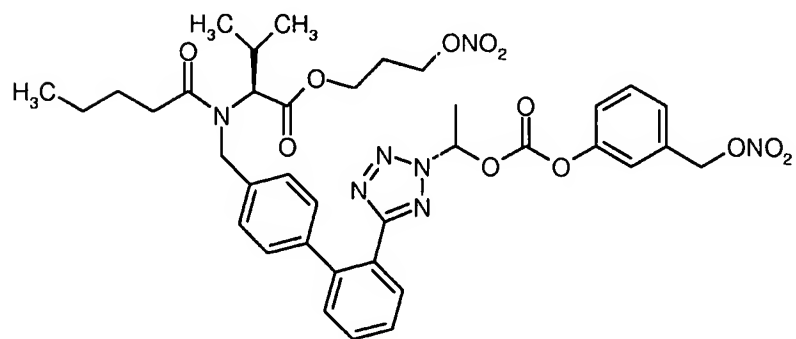


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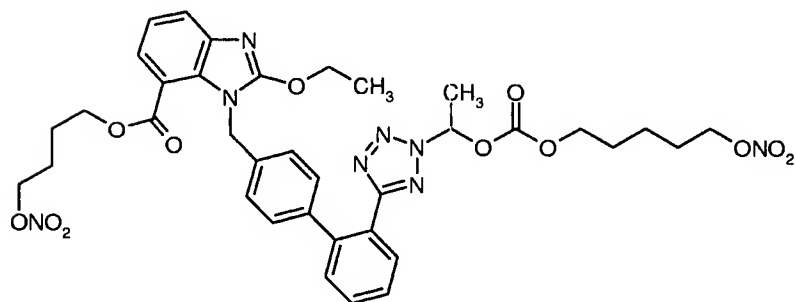
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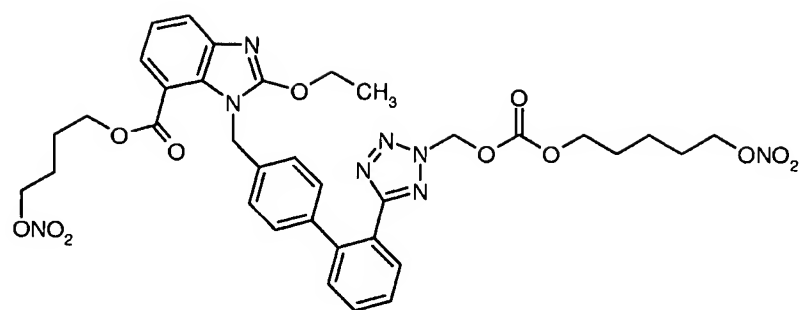
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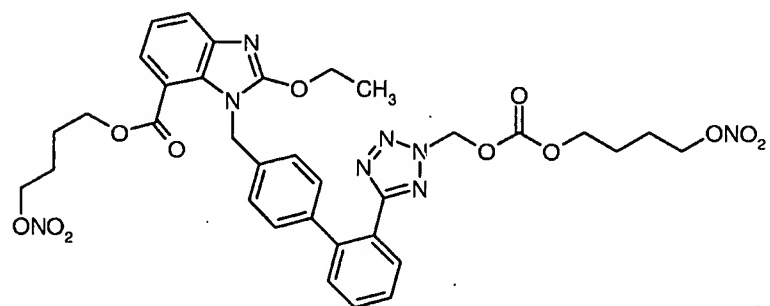
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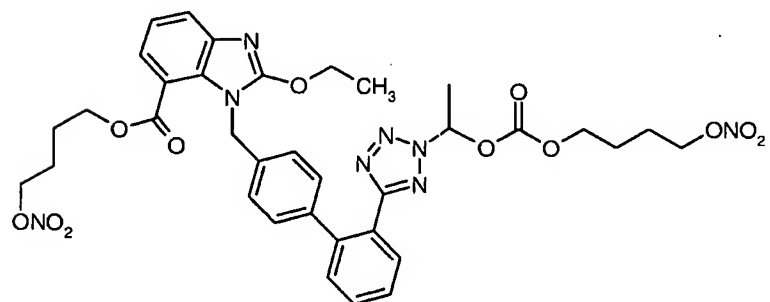
(471)



(472)

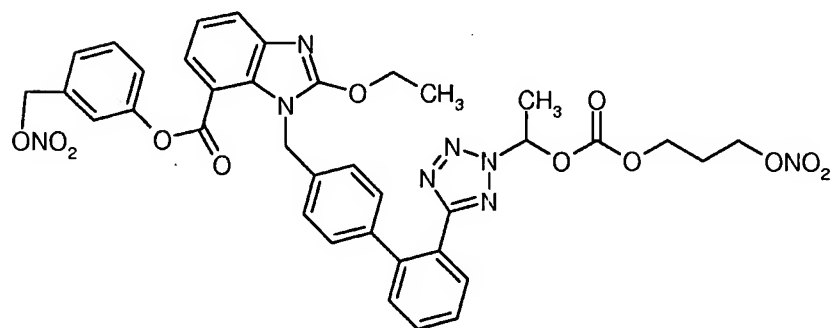


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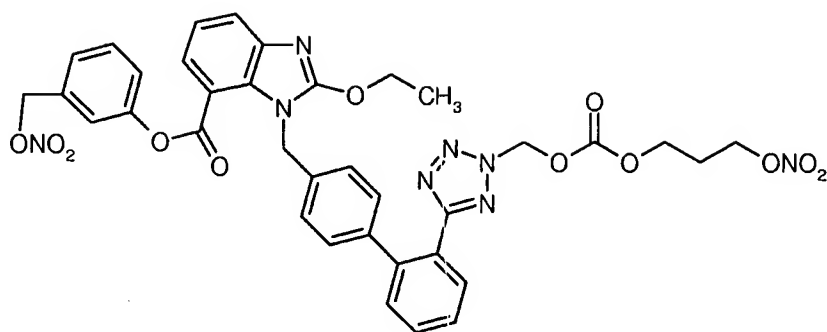


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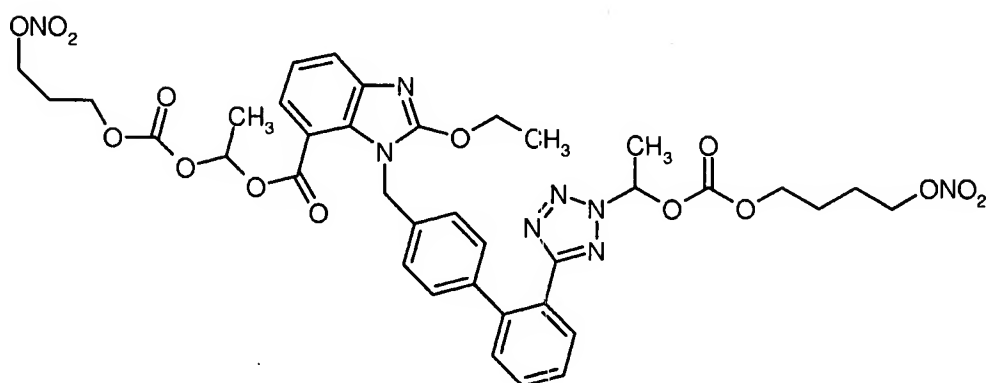
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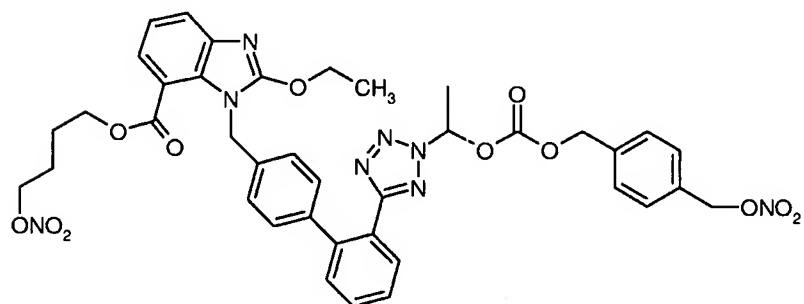
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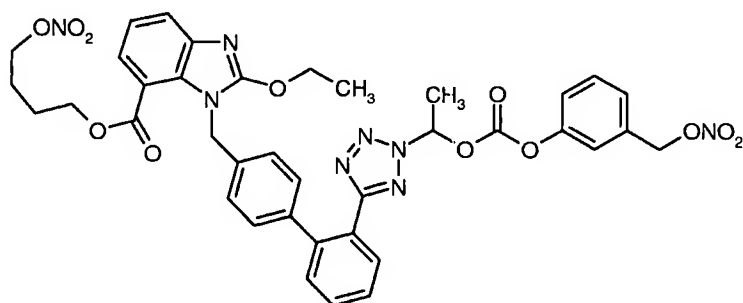


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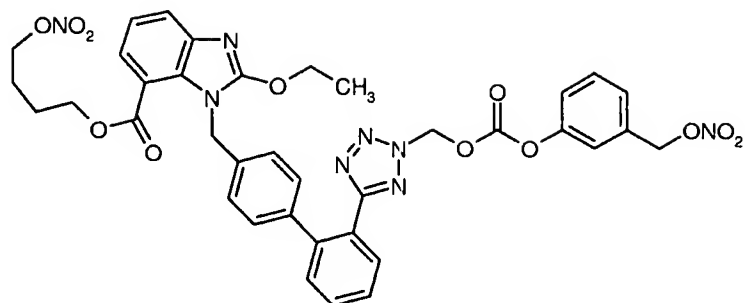


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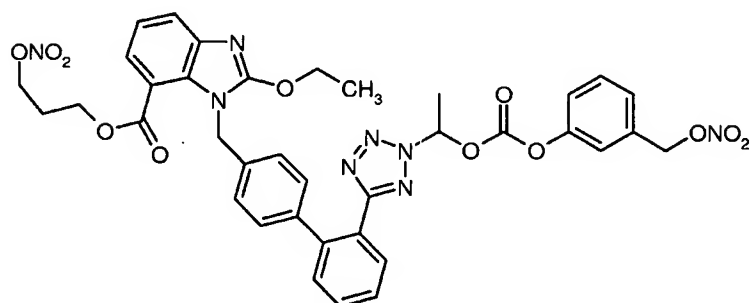
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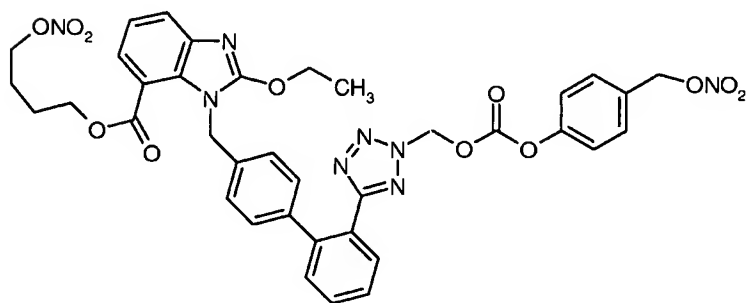


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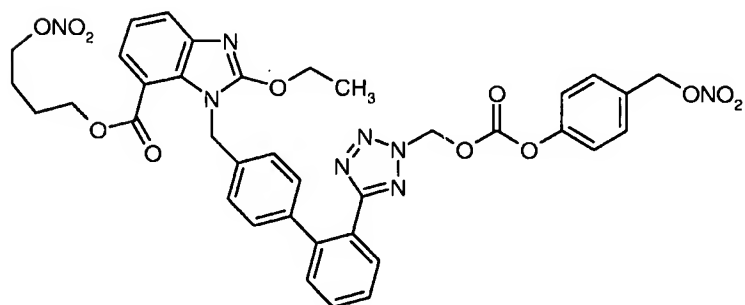


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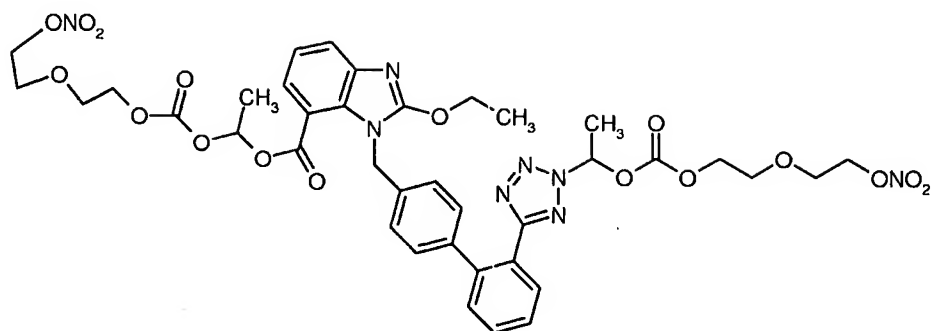
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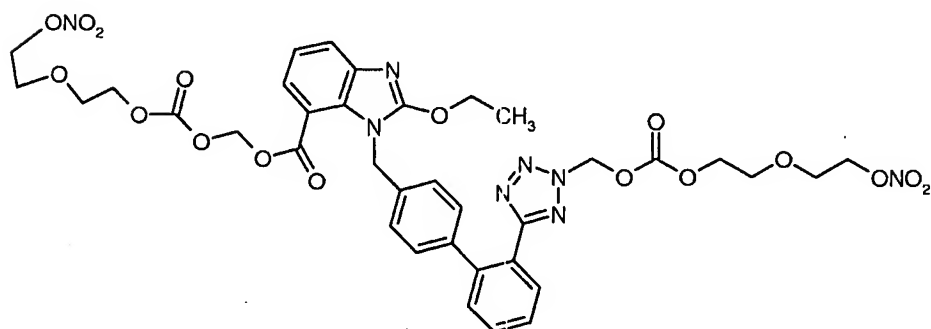
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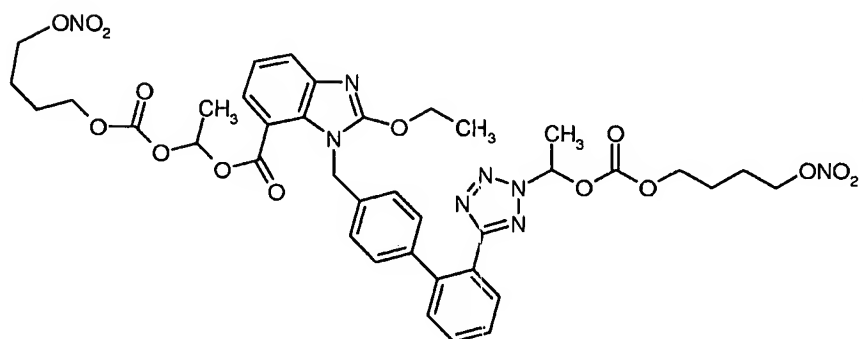
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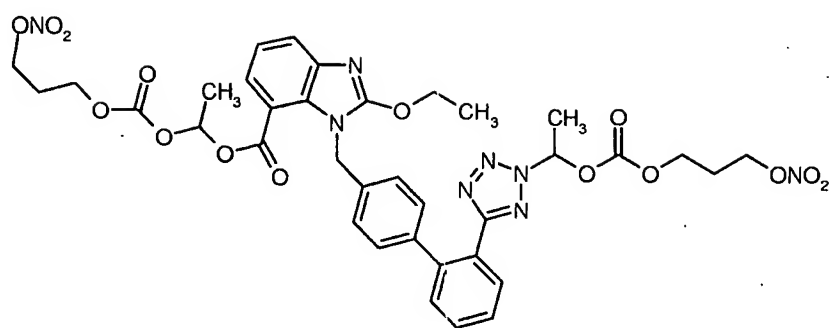
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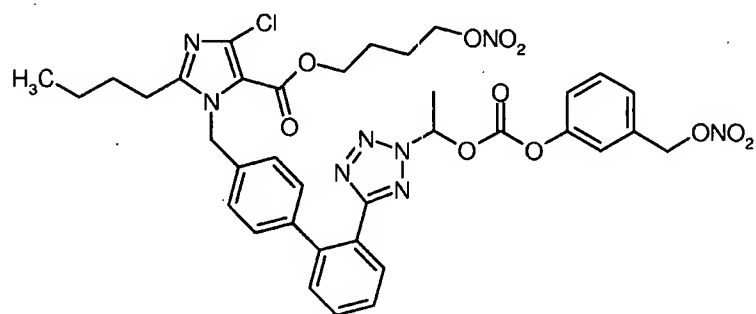
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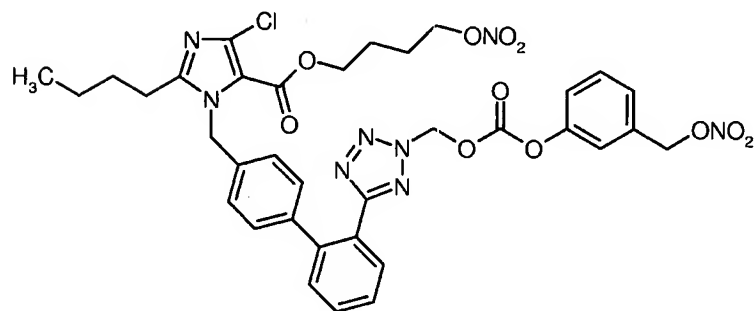
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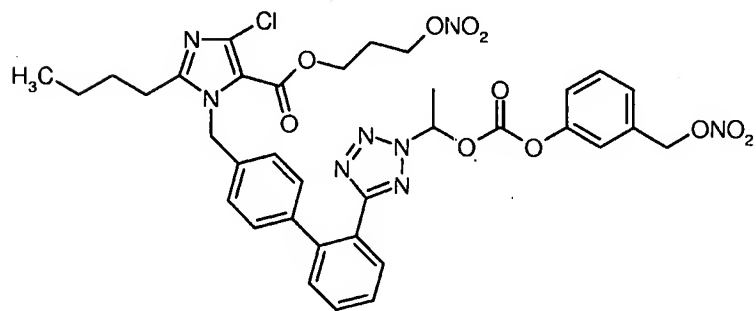
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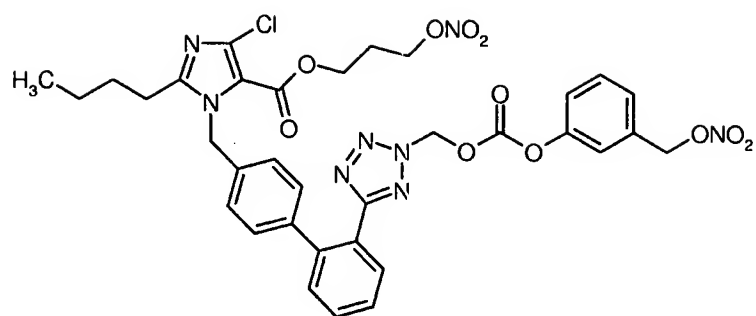
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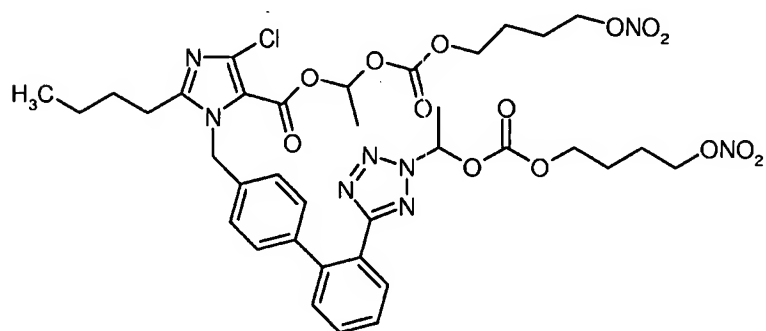
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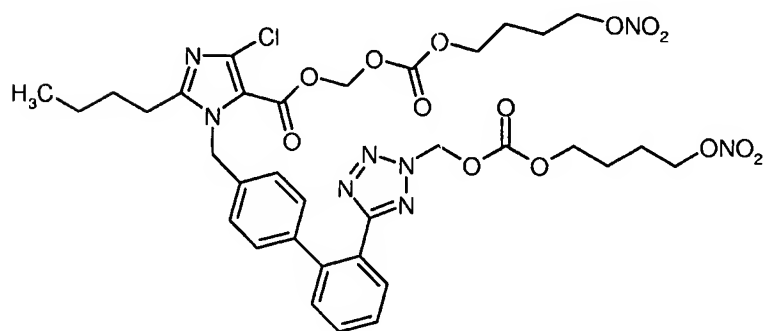
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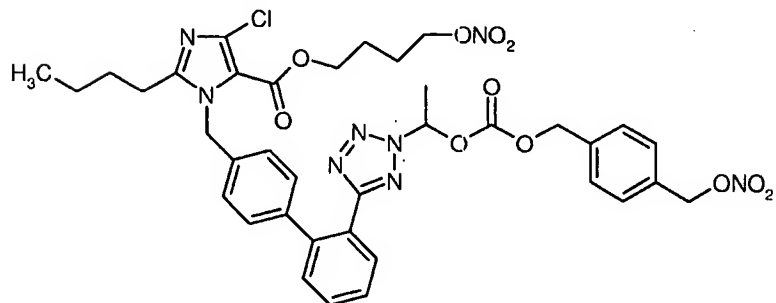
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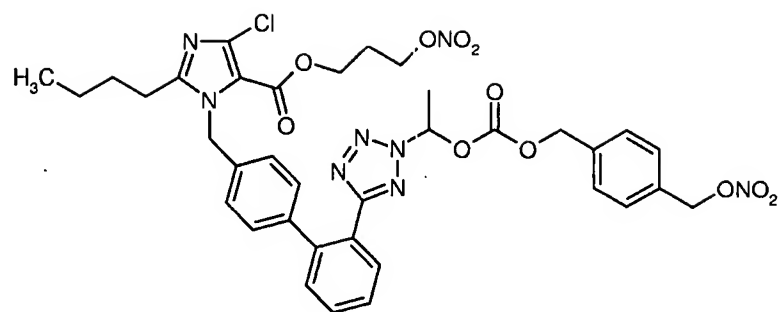
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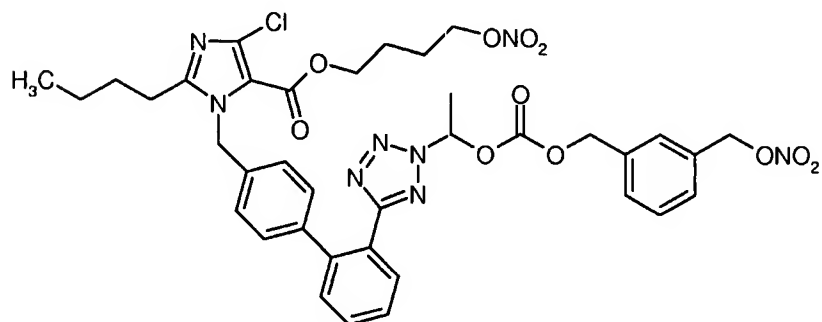
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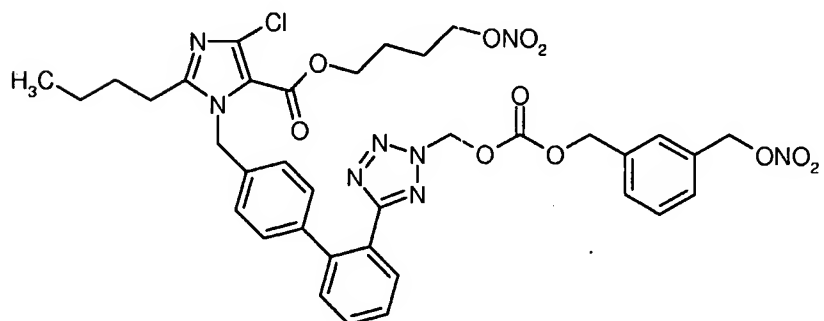
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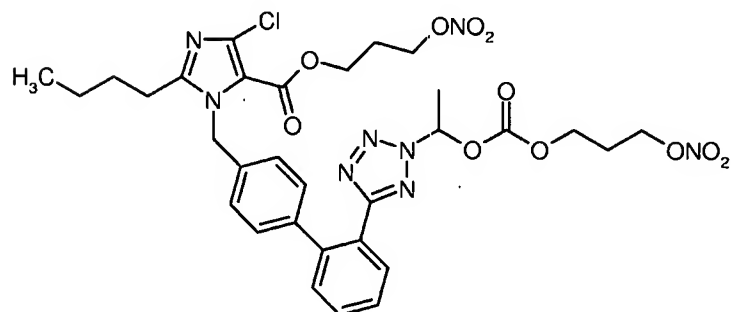
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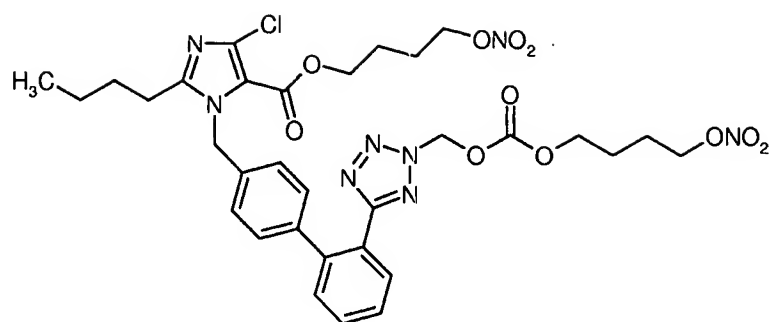
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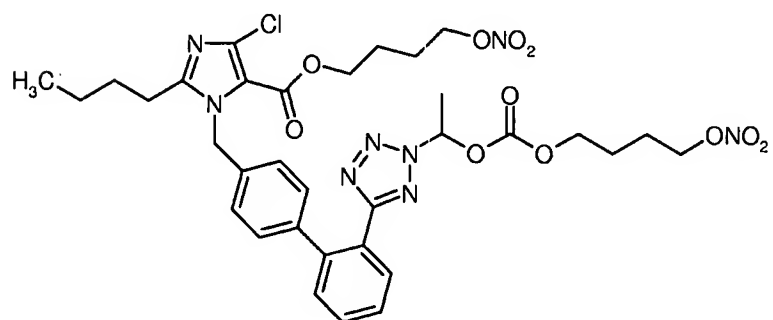
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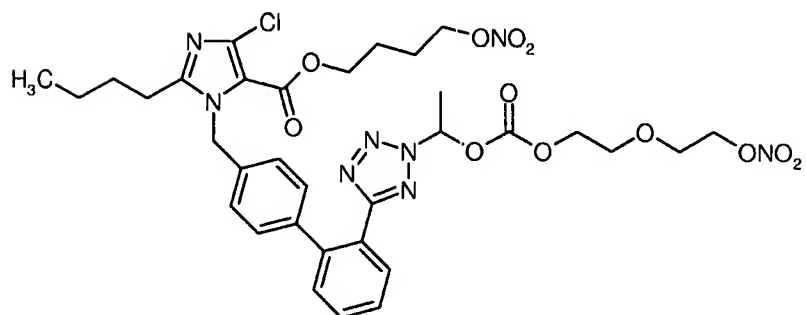
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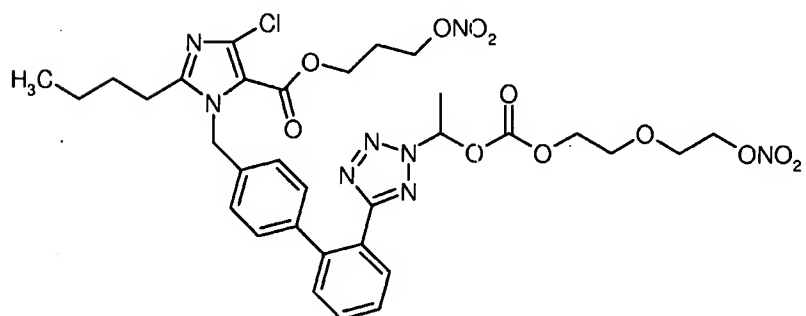
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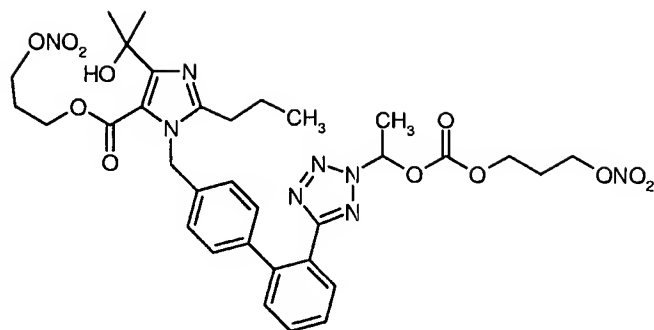


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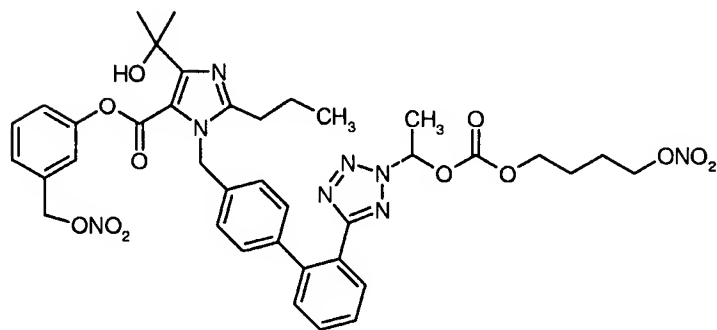


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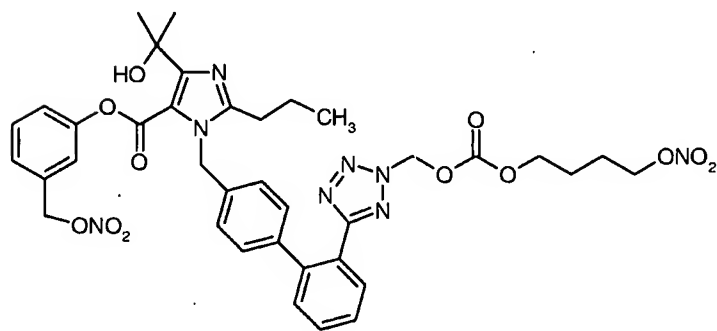


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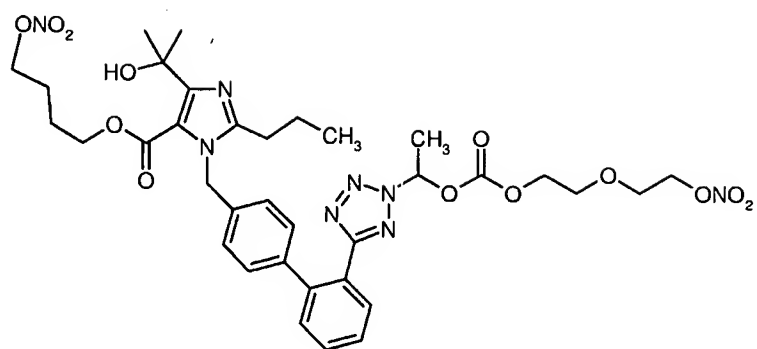


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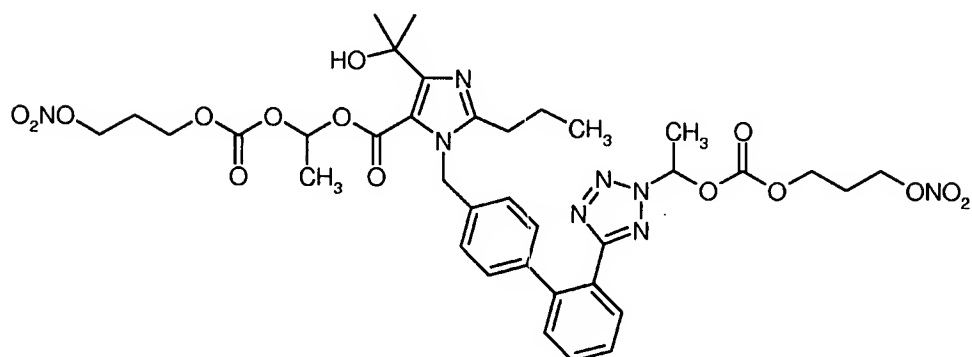
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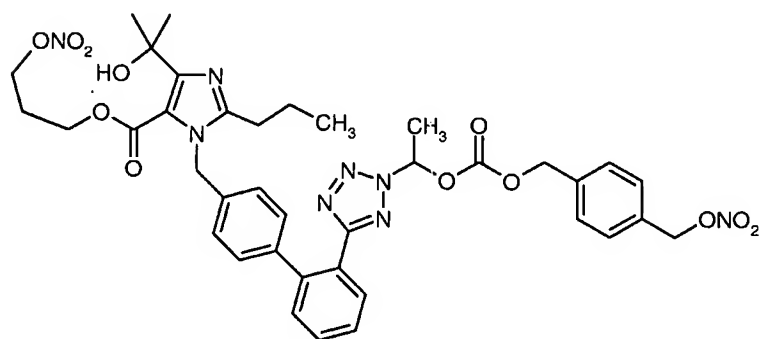
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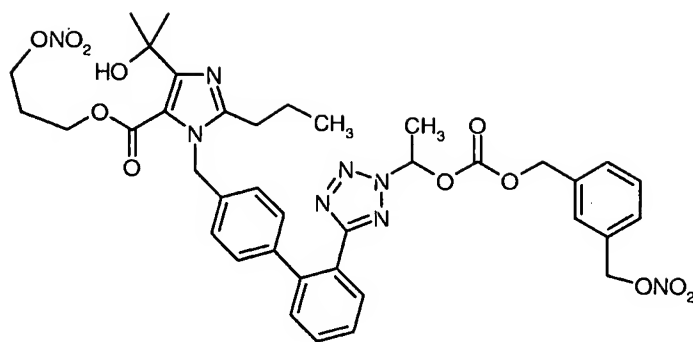
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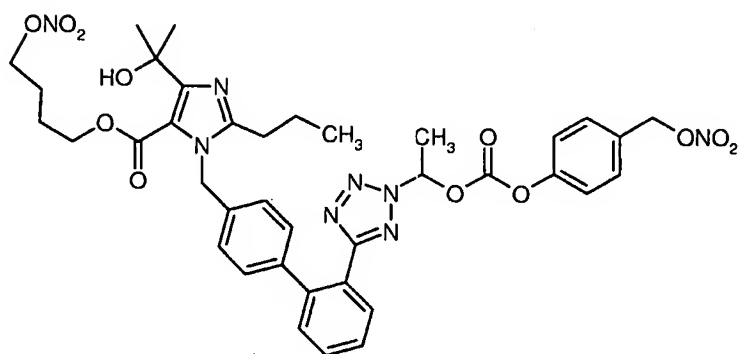
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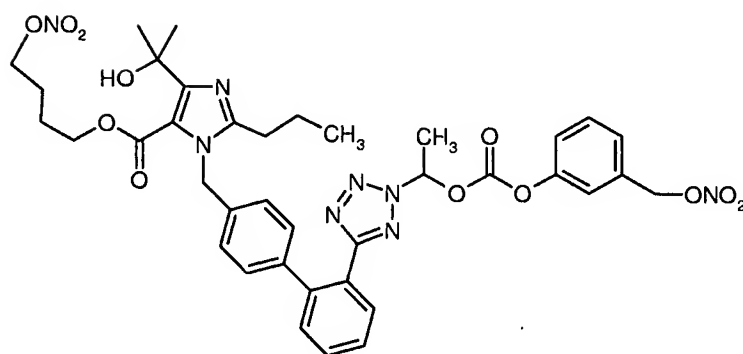


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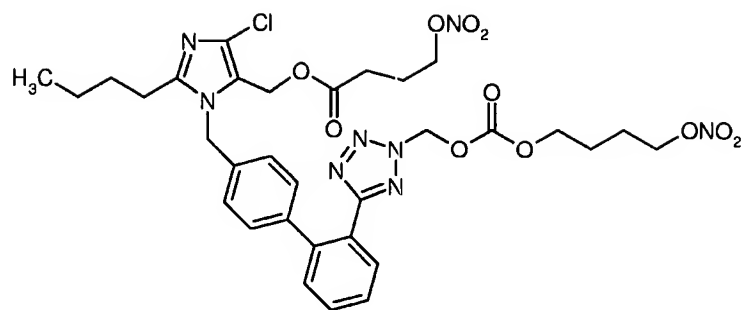


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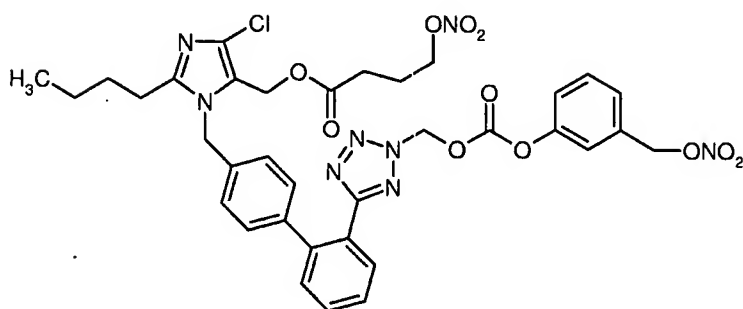
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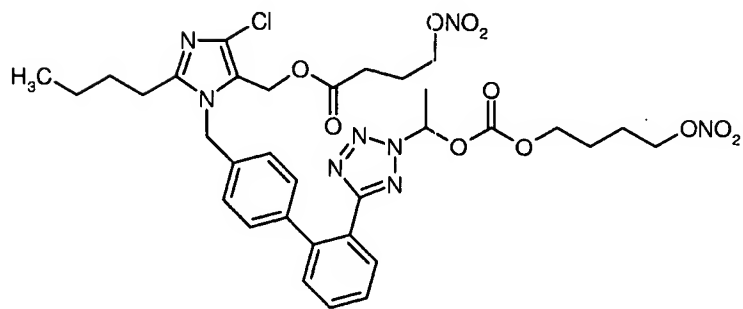
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The daily dose of active ingredient that should be administered can be a single dose or it can be an effective amount divided into several smaller doses that are to be

administered throughout the day. The dosage regimen and administration frequency for treating the mentioned diseases with the compound of the invention and/or with the pharmaceutical compositions of the present invention will
5 be selected in accordance with a variety of factors, including for example age, body weight, sex and medical condition of the patient as well as severity of the disease, route of administration, pharmacological considerations and eventual concomitant therapy with other
10 drugs.

The compounds of the invention may be administered orally, parenterally, rectally or topically, by inhalation or aerosol, in formulations eventually containing conventional non-toxic pharmaceutically acceptable
15 carriers, adjuvants and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular,
20 intrasternal injection or infusion techniques.

Injectable preparations, for example sterile injectable aqueous or oleaginous suspensions may be formulated according to known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable
25 preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents are water, Ringer's solution and isotonic sodium chloride. In addition, sterile, fixed oils are conventionally employed
30 as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or diglycerides, in addition fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the active ingredient with a suitable non-irritating excipient, such as cocoa butter and polyethylene glycols.

5 Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal
10 practice, additional substances other than inert diluents, e.g. lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

15 Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents,
20 emulsifying and suspending agents, and sweetening, flavouring and the like.

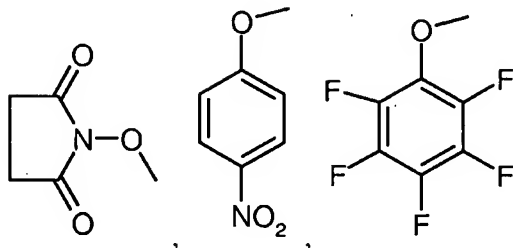
The compounds of the present invention can be synthesised as follows.

A) The compounds of general formula (I) wherein R_1 is
25 the radical (Ie), (If), (Ig), (Il), (Im) or (In), or R_1 is the radical of formulas (Ia), (Ib), (Ic) (Id) (Ih) or (Ii), wherein R_2 or R_3 are H, and wherein W is $-C(O)-$, and Y is as above defined, can be obtained by a process comprising:
1A) reacting compounds of formula (1a)

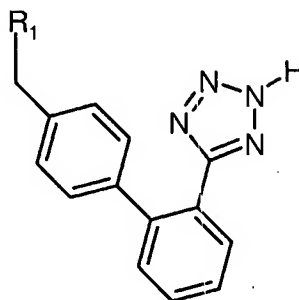
30
$$\text{Act-C(O)-Y-ONO}_2$$

(1a)

wherein Y are as above defined and wherein Act is a carboxylic acid activating group used in peptide chemistry such as:



5 with a compound of formula (1)



(1)

wherein:

R₁ is the radical of formulae (Ie), (If), (Ig), (Il) or
10 (Im), (In), or

R₁ is (Ia) wherein R₂ is H and the functional group -CH₂-OH is protected, or

R₁ is (Ib), (Ic), (Id), (Ih) or (Ii) wherein R₃ is H and the functional groups -C(O)OH are protected, in presence of
15 a inorganic or organic base/DMAP in an aprotic polar/non-polar solvent such as DMF, THF or CH₂Cl₂ at temperatures range between 0° to 65°C or in a double phase system H₂O/Et₂O at temperatures range between 20° to 40°C; or in the presence of DMAP and a Lewis acid such as Sc(OTf)₃ or
20 Bi(OTf)₃ in solvents such as DMF, CH₂Cl₂;

and then removing the protective group of the compounds obtained as described in 1A);

and optionally converting the resulting compound of general formula (I) into a pharmaceutically acceptable salt thereof.

1A.a) The compounds of formula (1) wherein R_1 is the radical (Ie), (If), (Ig), (Il), (Im) or (In), are commercially available or can be synthesised as follow:

- the compound of formula (1) wherein R_1 is the radical of formula (Ie) is known as Elisartan and is obtained as described in EP 535420;
- 10 - the compound of formula (1) wherein R_1 is the radical of formula (If) is known as Exp 3179 and is obtained as described in J. Med. Chem., 1991, 34, 2525-2547;
- the compound of formula (1) wherein R_1 is the radical of formula (Ig) is known as Olmesartan medoxomil and is
15 obtained as described in The Merck Index, Thirteenth Edition;
- the compound of formula (1) wherein R_1 is the radical of formula (Il) is known as Tasosartan and is obtained as described in The Merck Index, Thirteenth Edition;
- 20 - the compound of formula (1) wherein R_1 is the radical of formula (Im) is known as Irbesartan and is obtained as described in The Merck Index, Thirteenth Edition;
- the compound of formula (1) wherein R_1 is the radical of formula (In) is known as Candesartan Cilexetil and is
25 obtained as described in The Merck Index, Thirteenth Edition;

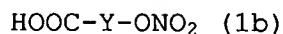
1A.b) The compound of formula (1) wherein R_1 is (Ia) and the functional group $-\text{CH}_2\text{-OH}$ is protected, is obtained by reacting the compound of formula (1) wherein R_1 is the
30 radical (Ia) and R_2 is H by conventional reaction to insert a protective group such as BOC according to well known reaction conditions.

The compound of formula (1) wherein R_1 is the radical of formula (Ia) and R_2 is H, is known as Losartan and is commercially available or is synthesised as described in The Merck Index, Thirteenth Edition;

- 5 1A.c) The compounds of formula (1), wherein R_1 is (Ib), (Ic), (Id), (Ih) or (Ii) and the functional groups $-C(O)OH$ are protected, are obtained by reacting compounds of formula (1) wherein R_1 is the radical of formulae (Ib), (Ic), (Ih) or (Ii) and R_3 is H, by conventional reaction to
10 insert a protective group such as trityl, benzyl, methyl according to well known reaction conditions;

The compounds of formula (1) wherein R_1 is the radical of formula (Ib), (Ic) (Id) (Ih) or (Ii), wherein R_3 is H, are commercially available or can be synthesised as follow:

- 15 - the compound of formula (1) wherein R_1 is the radical of formula (Ib) is known as Olmesartan and is obtained as described in The Merck Index, Thirteenth Edition;
- the compound of formula (1) wherein R_1 is the radical of formula (Ic) is known as EXP 3174 and is obtained as
20 described in Tetrahedron Letters, 44 (2003), 1149-1152;
- the compound of formula (1) wherein R_1 is the radical of formula (Id) is known as Dup 532 and is obtained as described in J. Org. Chem., 1993, 58, 4642.
- the compound of formula (1) wherein R_1 is the radical of
25 formula (Ih) is known as Valsartan and is obtained as described in The Merck Index, Thirteenth Edition;
- the compound of formula (1) wherein R_1 is the radical of formula (Ii) is known as Candesartan and is obtained as described in The Merck Index, Thirteenth Edition;
- 30 1A.d) The compounds of formula (1a) as above defined are obtained by reacting the acids (1b)



wherein Y is as above defined, with the commercially available compounds (1c)

Act-H (1c)

wherein Act is as above defined, by conventional esterification reaction with condensing agents as DCC
5 EDAC.HCl as well known in the literature.

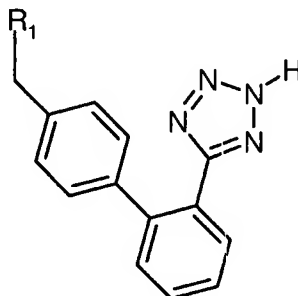
1A.e) The compounds of formula (1b) as above defined are obtained by reacting the commercially available acids of formula (1d)

10

Hal-Y-COOH (1d)

with AgNO₃ in a suitable organic solvent such as acetonitrile or tetrahydrofuran (THF) under nitrogen in the dark at temperatures range between 20° to 80°C; alternatively the reaction with AgNO₃ can be performed
15 under microwave irradiation in solvents such acetonitrile or THF at temperatures in the range between 70-180°C for short time (1-60 min).

B) The compounds of general formula (I) wherein R₁ is
20 the radical (Ie), (If), (Ig), (Il), (Im) or (In), or R₁ is the radical of formulas (Ia), (Ib), (Ic) (Id) (Ih) or (Ii), wherein R₂ or R₃ are H, and wherein W is -C(O)O- and Y is as above defined, can be obtained by a process comprising:
1B) reacting compounds of formula (1)



25

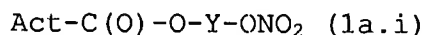
(1)

wherein:

R_1 is the radical of formulae (Ie), (If), (Ig), (Il) or (Im), (In), or

R_1 is (Ia) wherein R_2 is H and the functional group $-CH_2-OH$ is protected, or

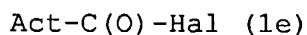
- 5 R_1 is (Ib), (Ic), (Id), (Ih) or (Ii) wherein R_3 is H and the functional groups $-C(O)OH$ are protected, with a compound of formula (1a.i)



- wherein Act and Y are as above defined, in presence of a
 10 inorganic or organic base/DMAP in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0° to $65^\circ C$ or in a double phase system H_2O/Et_2O at temperatures range between 20° to $40^\circ C$; or in the presence of DMAP and a Lewis acid such as $Sc(OTf)_3$ or
 15 $Bi(OTf)_3$ in solvents such as DMF, CH_2Cl_2 ;

and then removing the protective group of the compounds obtained as described in 1B); and optionally converting the resulting compounds of formula (I) into a pharmaceutically acceptable salt.

- 20 1B.a) The compounds of formula (1a.i) as above defined are obtained by reacting compounds of formula (1e)



with a compounds of formula (1f)



- 25 wherein Y is as above defined, in presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0° to $65^\circ C$ or in a double phase system H_2O/Et_2O at temperatures range between 20° to $40^\circ C$,

- 30 1B.b) The compounds of formula (1f) are obtained by reacting the commercially available compounds of formula $HO-Y-Hal$ (1f') wherein Y and Hal are as above defined, with $AgNO_3$ in a suitable organic solvent such as acetonitrile or

tetrahydrofuran (THF) under nitrogen in the dark at temperatures range between 20°-80°C; alternatively the reaction with AgNO₃ can be performed under microwave irradiation in solvents such acetonitrile or THF at
5 temperatures in the range between about 100-180°C for time range about 1-60 min.

The compounds of formula (1f') are commercially available or can be obtained by method well known in the literature; 1B.d) The compounds of formula (1e) as above defined are
10 obtained by reacting compounds of formula (1c)

Act-H (1c)

wherein Act is as above defined, with phosgene and derivatives such as triphosgene, in the presence of a inorganic or organic base in an aprotic polar/non-polar
15 solvent such as DMF, THF or CH₂Cl₂ at temperatures range between 0° to 65°C.

C) Alternatively, the compounds of general formula (I) wherein R₁ is the radical (Ie), (If), (Ig), (Il), (Im) or
20 (In), or R₁ is the radical of formulas (Ia), (Ib), (Ic) (Id) (Ih) or (Ii) wherein R₂ or R₃ are H, and wherein W is -C(O)O-, and Y is as above defined, can be obtained by a process comprising:

1C) reacting compounds of formula (1) wherein:

25 R₁ is the radical of formulae (Ie), (If), (Ig), (Il) or (Im), (In), or

R₁ is (Ia) wherein R₂ is H and the functional group -CH₂-OH is protected, or

R₁ is (Ib), (Ic), (Id), (Ih) or (Ii) wherein R₃ is H and
30 the functional groups -C(O)OH are protected,
with compounds of formula (1a.ii),

Hal-C(O)-O-Y-ONO₂ (1a.ii)

wherein Hal is an halogen atom, preferably is Cl, and Y is as above defined, in presence of a inorganic or organic base/DMAP in an aprotic polar/non-polar solvent such as DMF, THF or CH₂Cl₂ at temperatures range between 0° to 65°C
5 or in a double phase system H₂O/Et₂O at temperatures range between 20° to 40°C; or in the presence of DMAP and a Lewis acid such as Sc(OTf)₃ or Bi(OTf)₃ in solvents such as DMF, CH₂Cl₂; and then removing the protective group of the obtained compounds; and optionally converting the resulting
10 compounds of formula (I) into a pharmaceutically acceptable salt.

1C.a) The compound of formula (1) wherein R₁ is (Ia) and the functional group -CH₂-OH is protected, is obtained as described in 1A.b).

15 The compounds of formula (1), wherein R₁ is (Ib), (Ic), (Id), (Ih) or (Ii) and the functional groups -C(O)OH are protected, are obtained as described in 1A.c).

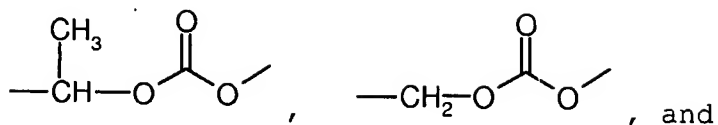
1C.b) The compounds of formula (1a.ii) as above defined, are obtained by reacting a compounds of formula(1f)

20 HO-Y-ONO₂ (1f)

and phosgene and its derivatives such as triphosgene in the presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH₂Cl₂ at temperatures range between 0° to 65°C,

25 1C.c) The compounds of formula (1f) are obtained as described in 1B.b).

D) Alternatively, the compounds of general formula (I) wherein R₁ is the radical (Ie), (If), (Ig), (Il), (Im) or
30 (In), or R₁ is the radical of formulas (Ia), (Ib), (Ic) (Id) (Ih) or (Ii), wherein R₂ or R₃ are H, and wherein W is,



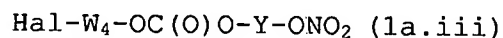
Y is as above defined, can be obtained by a process comprising:

1D) reacting compounds of formula (1) wherein:

5 R₁ is the radical of formulae (Ie), (If), (Ig), (Il) or (Im), (In), or

R₁ is (Ia) wherein R₂ is H and the functional group -CH₂-OH is protected, or

R₁ is (Ib), (Ic), (Id), (Ih) or (Ii) wherein R₃ is H and
10 the functional groups -C(O)OH are protected,
with compounds of formula (1a.iii)



wherein Hal is an halogen atom and W₄ is -CH₂- or -CH(CH₃)-,
in presence of a inorganic or organic base in an aprotic
15 polar/non-polar solvent such as DMF, THF or CH₂Cl₂ at
temperatures range between 0° to 65°C or in a double phase
system H₂O/Et₂O at temperatures range between 20° to 40°C;
and then removing the protective group of the obtained
compounds.

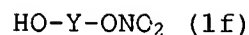
20 1D.a) The compound of formula (1) wherein R₁ is (Ia) and
the functional group -CH₂-OH is protected, is obtained
using method described in 1A.b).

The compounds of formula (1), wherein R₁ is (Ib), (Ic),
(Id), (Ih) or (Ii) and the functional groups -C(O)OH are
25 protected, are obtained using the method described in
1A.c).

1D.b) The compounds of formula (1a.iii) are obtained by
reacting the commercially available haloalkylhalocarbonate
of formula (1g)



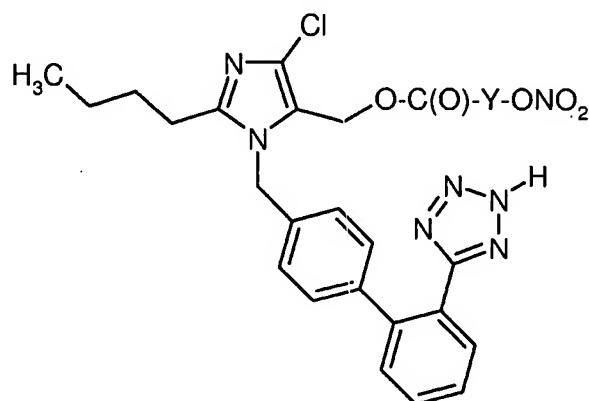
wherein Hal and W₄ are as above defined, with a compound of
formula (1f)



wherein Y is as above defined, in the presence of a inorganic or organic base in an aprotic polar or in an aprotic non-polar solvent such as DMF, THF or CH_2Cl_2 at
 5 temperatures range between 0° to 65°C ,
 1D.b) The compounds of formula (1f) are obtained as described in 1B.b).

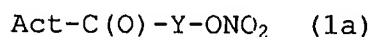
E) Compounds of general formula (I) wherein R_1 is (1a),
 10 wherein R_2 is $-\text{C}(\text{O})-\text{Y}-\text{ONO}_2$, and wherein W is $-\text{C}(\text{O})-$, and Y is as above defined, can be obtained by a process comprising:

1E) reacting compounds of formula (2b)



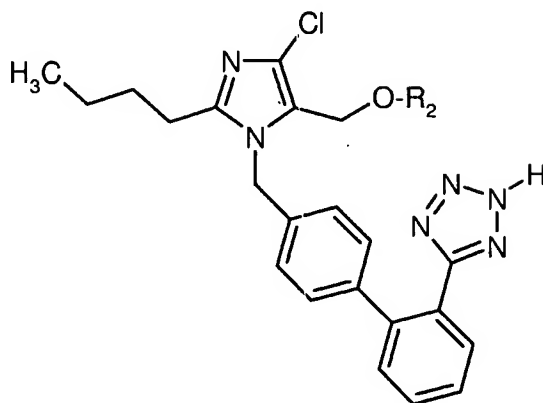
15 (2b)

wherein Y is as above defined, with compounds of formula (1a)



wherein Act and Y are as above reported, in presence of a inorganic or organic base/DMAP in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures
 20 range between 0° to 65°C or in a double phase system $\text{H}_2\text{O}/\text{Et}_2\text{O}$ at temperatures range between 20° to 40°C ; or in the presence of DMAP and a Lewis acid such as $\text{Sc}(\text{OTf})_3$ or
 25 $\text{Bi}(\text{OTf})_3$ in solvents such as DMF, CH_2Cl_2 .

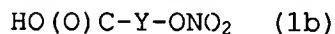
1E.a) The compounds of formula (2b) are obtained by reacting a compounds of formula (2)



(2)

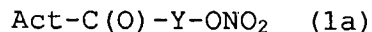
5

wherein R₂ is H, with a compound of formula (1b)



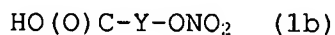
according to the method described in the literature Maria C. Breschi et al., Journal of Medicinal Chemistry, 47 (23),
10 5597-5600, 2004.

1E.b) The compounds of formula (1a)



as above defined, are obtained by using the method described in 1A.d).

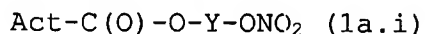
15 1E.c) The compound of formula (1b)



as above defined, are obtained by using the method described in 1A.e).

20 F) Compounds of general formula (I) wherein R₁ is (1a), wherein R₂ is -C(O)-Y-ONO₂, and wherein W is -C(O)O-, and Y is as above defined, can be obtained by a process comprising:

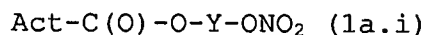
1F) reacting a compounds of formula (2b) above defined,
25 with compounds of formula (1a.i)



wherein Act and Y are as above reported, in presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH₂Cl₂ at temperatures range between 0° to 65°C or in a double phase system H₂O/Et₂O at
 5 temperatures range between 20° to 40°C; or in the presence of DMAP and a Lewis acid such as Sc(OTf)₃ or Bi(OTf)₃ in solvents such as DMF, CH₂Cl₂.

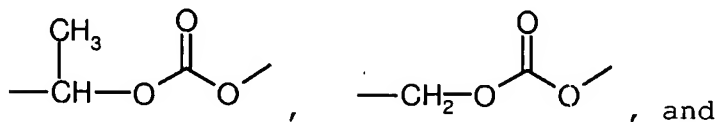
1F.a) The compounds of formula (2b) are obtained using method described in 1E.a).

10 1F.b) The compounds of formula (1a.i)



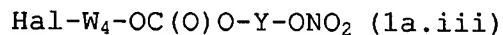
as above defined, are obtained as described in 1B.a).

G) Compounds of general formula (I) wherein R₁ is (Ia)
 15 wherein R₂ is -C(O)-Y-ONO₂, and wherein W is



Y is as above defined, can be obtained by a process comprising:

1G) reacting a compounds of formula (2b) with compounds of
 20 formula (1a.iii)



wherein Hal, W₄, Y are as above reported, in presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH₂Cl₂ at temperatures range
 25 between 0° to 65°C or in a double phase system H₂O/Et₂O at temperatures range between 20° to 40°C;

1G.a) The compounds of formula (2b) are obtained by using method described in 1E.a).

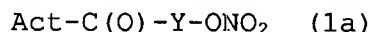
1G.b) The compounds of formula (1a.iii)

30 $\text{Hal-W}_4\text{-OC(O)O-Y-ONO}_2 \text{ (1a.iii)}$

as above reported are obtained by using method described in 1D.b).

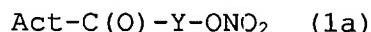
H) Compounds of formula (I) wherein R_1 is (Ib), (Ic), (Id), (Ih) or (Ii), wherein R_3 is $-Y-ONO_2$, and wherein W is $-C(O)-$, and Y is as above defined, can be obtained by
5 a process comprising:

1H) reacting compounds of formula (1) wherein R_1 is as above reported and R_3 is $-Y-ONO_2$, with compounds of formula (1a)



10 wherein Act and Y are as above reported, in presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0° to $65^\circ C$ or in a double phase system H_2O/Et_2O at temperatures range between 20° to $40^\circ C$; or in the presence
15 of DMAP and a Lewis acid such as $Sc(OTf)_3$ or $Bi(OTf)_3$ in solvents such as DMF, CH_2Cl_2 .

1H.a) The compounds of formula (1a)



as above defined are obtained by using the method described
20 in 1A.d).

1H.b) The compounds of formula (1) wherein R_1 is as above reported and R_3 is $-Y-ONO_2$ are obtained by reacting compounds of formula (1), wherein R_1 is (Ib), (Ic), (Id), (Ih) or (Ii) and R_3 is H, with compounds of formula (1f)

25 $HO-Y-ONO_2$ (1f)

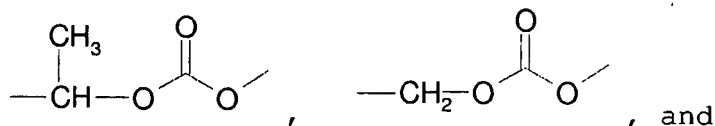
wherein Y is as above reported, in presence of a condensing agent such as DCC or EDAC.

1H.c) The compounds of formula (1f)



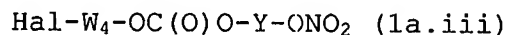
30 wherein Y is as above reported, can be prepared for example as described in Shan et al., Journal of Medicinal Chemistry, 47, 254-261, 2004.

I) Compounds of formula (I) wherein R_1 is (Ib), (Ic), (Id), (Ih) or (Ii), wherein R_3 is $-Y-ONO_2$, and wherein W is



Y is as above defined, can be obtained by a process comprising:

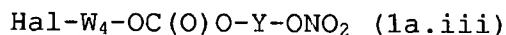
1I) reacting compounds of formula (1) wherein R_1 is as above reported and R_3 is $-Y-ONO_2$, with compounds of formula (1a.iii)



wherein W_4 is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$ and Hal is an halogen atom, Y is as above reported, in presence of an inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0° to 65°C ;

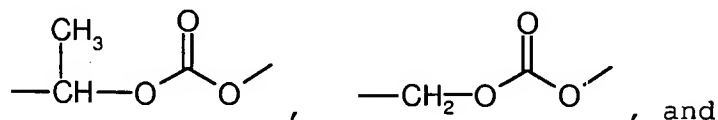
1I.a) The compounds of formula (1) wherein R_1 is as above reported and R_3 is $-Y-ONO_2$ are obtained by method described in 1H.b).

1I.b) The compounds of formula (1a.iii)



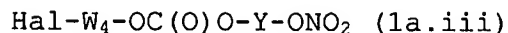
as above defined, are obtained by method described in 1D.b).

L) Compounds of formula (I) wherein R_1 is (Ib), (Ic), (Id), (Ih) or (Ii), wherein R_3 is $-W_2-Y-ONO_2$, and wherein W_2 and W are



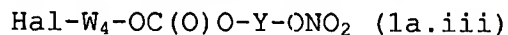
Y is as above defined, can be obtained by a process comprising:

1L) reacting a compounds of formula (1), wherein R_1 is (Ib), (Ic), (Id), (Ih) or (Ii) and R_3 is H, with compounds of formula (1a.iii)



5 wherein W_4 is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$ and Hal is an halogen atom, Y is as above reported, in presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0° to 65°C .

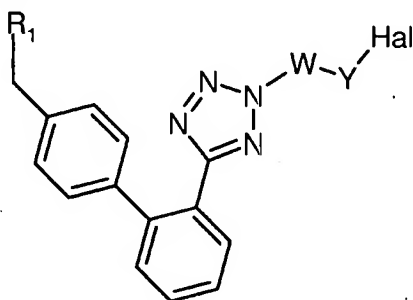
10 1L.a) The compounds of formula (1a.iii)



wherein W_4 , Hal and Y are as above reported, are obtained by method described in 1D.b).

15 M) Alternatively the compounds of general formula (I) wherein R_1 is the radical (Ie), (If), (Ig), (Il), (Im) or (In), or R_1 is the radical of formulas (Ia), (Ib), (Ic) (Id) (Ih) or (Ii) wherein R_2 or R_3 are H, and wherein W is $-\text{C(O)}$ or $-\text{C(O)O}-$, and Y is as above defined, can be
20 obtained by a process comprising:

1M) reacting a compound of formula (3)



(3)

wherein:

25 R_1 is the radical (Ie), (If), (Ig), (Il), (Im) or (In), or R_1 is the radical of formula (Ia) wherein R_2 is H and the functional group $-\text{CH}_2\text{-OH}$ is protected, or

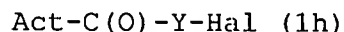
R₁ is (Ib), (Ic), (Id), (Ih) or (Ii) wherein R₃ is H and the functional groups -C(O)OH are protected;

W and Y are as above defined, Hal is an halogen atom, preferably Cl, Br, I, with AgNO₃ as described for similar transformations;

and then removing the protective group with the methods known in the art; and optionally converting the resulting compound of general formula (I) into a pharmaceutically acceptable salt.

1M.a) The compounds of formula (3) as above defined are obtained by reacting compounds of formula (1) wherein R₁ is the radical (Ie), (If), (Ig), (Il), (Im) or (In), or R₁ is the radical of formula (Ia) wherein R₂ is H and the functional group -CH₂-OH is protected, or

R₁ is (Ib), (Ic) (Id) (Ih) or (Ii) wherein R₃ is H and the functional groups -C(O)OH are protected, with compounds of formula (1h)



or compounds of formula (1l)

Act-C(O)-O-Y-Hal (1l)

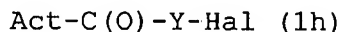
wherein Hal is an halogen atom and Act, Y are as above defined, in presence of a inorganic or organic base/DMAP in an aprotic polar/non-polar solvent such as DMF, THF or CH₂Cl₂ at temperatures range between 0° to 65°C or in a double phase system H₂O/Et₂O at temperatures range between 20° to 40°C; or in the presence of DMAP and a Lewis acid such as Sc(OTf)₃ or Bi(OTf)₃ in solvents such as DMF, CH₂Cl₂;

1M.b) The compound of formula (1) wherein R₁ is (Ia) and the functional group -CH₂-OH is protected, is obtained using method described in 1A.b).

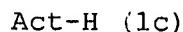
The compounds of formula (1), wherein R₁ is (Ib), (Ic), (Id), (Ih) or (Ii) and the functional groups -C(O)OH are

protected, are obtained using the method described in 1A.c).

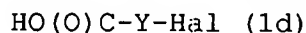
1M.b) The compounds of formula (1h)



5 as above defined, are obtained by reacting commercially available (1c)

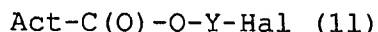


with the commercially available compounds of formula (1d)

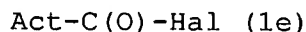


10 by conventional esterification reaction with condensing agents as DCC EDAC.HCl as well known in the literature.

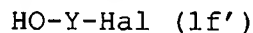
The compounds of formula (1l)



as above defined, are obtained by reacting compounds of 15 formula(1e)



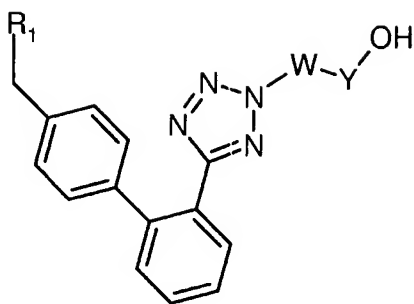
which are commercially available or are obtained as described in 1B.d), with a compounds of formula(1f')



20 in presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH₂Cl₂ at temperatures range between 0° to 65°C or in a double phase system H₂O/Et₂O at temperatures range between 20° to 40°C;

25 N) Alternatively the compounds of general formula (I) wherein R₁ is the radical (Ie), (If), (Ig), (Il), (Im) or (In), or R₁ is the radical of formulas (Ia), (Ib), (Ic) (Id) (Ih) or (Ii), wherein R₂ or R₃ are H, and wherein W is -C(O) or -C(O)O-, and Y is as above defined, can be 30 obtained by a process comprising:

1N) reacting a compounds of formula (4):



(4)

wherein:

R_1 is the radical (Ie), (If), (Ig), (Il), (Im) or (In), or

5 R_1 is the radical of formula (Ia) wherein R_2 is H and the functional group $-CH_2-OH$ is protected, or

R_1 is (Ib), (Ic), (Id), (Ih) or (Ii) wherein R_3 is H and the functional groups $-C(O)OH$ are protected,

W and Y are as above defined, with triflic
10 anhydride/tetraalkylammonium nitrate salt in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between -60° to $65^\circ C$;

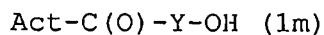
and then removing the protective group with the methods known in the art; and optionally converting the compound of
15 formula (I) into a pharmaceutically acceptable salt.

2N) The compounds of formula (4) are obtained by reacting the compounds of formula (1) wherein

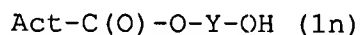
R_1 is the radical (Ie), (If), (Ig), (Il), (Im) or (In), or

20 R_1 is the radical of formula (Ia) wherein R_2 is H and the functional group $-CH_2-OH$ is protected, or

R_1 is (Ib), (Ic), (Id), (Ih) or (Ii) wherein R_3 is H and the functional groups $-C(O)OH$ are protected, with compounds of formula (1m)



25 or with compounds of formula (1n)



wherein Act and Y are as above defined, in presence of a inorganic or organic base/DMAP in an aprotic polar/non-

polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0° to 65°C or in a double phase system $\text{H}_2\text{O}/\text{Et}_2\text{O}$ at temperatures range between 20° to 40°C ; or in the presence of DMAP and a Lewis acid such as $\text{Sc}(\text{OTf})_3$ or

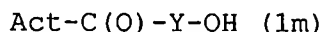
5 $\text{Bi}(\text{OTf})_3$ in solvents such as DMF, CH_2Cl_2 ;

2N.a) The compound of formula (1) wherein R_1 is (Ia) and the functional group $-\text{CH}_2-\text{OH}$ is protected, is obtained as described in 1A.b).

The compounds of formula (1), wherein R_1 is (Ib), (Ic),

10 (Id), (Ih) or (Ii) and the functional groups $-\text{C}(\text{O})\text{OH}$ are protected, are obtained as described in 1A.c).

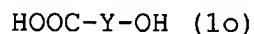
2N.b) The compounds of formula (1m)



are obtained by reacting commercially available (1c)

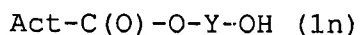
15 $\text{Act}-\text{H} \text{ (1c)}$

with the commercially available compounds of formula (1o)

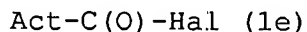


by conventional esterification reaction with condensing agents as DCC EDAC.HCl as well known in the literature;

20 The compounds of formula (1n)

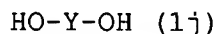


are obtained by reacting compounds of formula(1e)



which are commercially available or are obtained as

25 described in 1B.d), with a compounds of formula(1j)



in presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0° to 65°C or in a double phase

30 system $\text{H}_2\text{O}/\text{Et}_2\text{O}$ at temperatures range between 20° to 40°C ;

EXAMPLES

Example 1

Synthesis of 4-(nitrooxy)butanoic acid pentafluorophenyl ester

To a mixture of pentafluorophenol (3.3 g, 17.96 mmol),
5 4-bromobutanoic acid (3.0 g, 17.96 mmol) and DMAP (0.440 g,
3.59 mmol) in CH₂Cl₂ (30 ml), cooled to 0°C, EDAC.HCl (5.2
g, 26.94 mmol) was added in portion. The mixture was then
stirred at 0°C for 30 minutes. Then it was gradually warmed
to room temperature and stirred for 8 hrs. Then the mixture
10 was diluted with NaH₂PO₄ aqueous (5%, 50 ml) and acidified
with HCl 1N to pH 3-4. The organic phase was separated and
the aqueous phase was extracted with CH₂Cl₂ (2 x 50 ml).
The organic phase was washed with brine, dried over Na₂SO₄
and evaporated to give an oil that was purified by flash
15 chromatography (n-Hexane/EtOAc 98:2) to yield 4-
bromobutanoic acid pentafluorophenyl ester (5.2 g, 86%) as
a colorless oil.

A mixture of 4-bromobutanoic acid pentafluorophenyl ester
20 (5.2 g, 15.61 mmol) and AgNO₃ (6.6 g, 39.03 mmol) in CH₃CN
was heated at 60°C for 5 hrs under nitrogen, in the dark.
Then the mixture was cooled, concentrated and diluted with
EtOAc. The silver salts were filtered off, the solvent
evaporated. After flash chromatography purification (n-
25 Hexane/EtOAc 95:5) 4-(nitrooxy)butanoic acid
pentafluorophenyl ester (3.9 g, 80%) was obtained as a
colorless oil.

¹H NMR (CDCl₃) δ: 4.60(2H,t), 2.86(2H,t), 2.23(2H,m).

30

Example 2

Synthesis of 4-(nitrooxymethyl)benzoic acid pentafluoro-
phenyl ester

Starting from 4-(bromomethyl)benzoic acid (5.0 g, 23.25 mmol) and pentafluorophenol (4.3 g, 23.25 mmol), applying the same procedure described in Example 1, 4-(bromomethyl)benzoic acid pentafluorophenyl ester (5.0 g, 56%) was obtained as a solid.

From 4-(bromomethyl)benzoic acid pentafluorophenyl ester (5.0 g, 13.12 mmol) and AgNO₃ (5.6 g, 32.80 mmol), heating to reflux and applying the same procedure described in Example 1, after flash chromatography purification (n-Hexane/EtOAc 95:5) 4-(nitrooxymethyl)benzoic acid pentafluorophenyl ester (4.2 g, 88%) was obtained as a white solid.

m.p. 75-76°C

¹H NMR (CDCl₃) δ: 8.26 (2H, d), 7.60 (2H, d), 5.50 (2H, s).

Example 3

Synthesis of 5-(nitrooxy)pentanoic acid pentafluorophenyl ester

Starting from 5-bromopentanoic acid (1.0 g, 5.52 mmol) and pentafluorophenol (1.0 g, 5.52 mmol), applying the same procedure described in Example 1, 5-bromopentanoic acid pentafluorophenyl ester (1.5 g, 78%) was obtained as a colorless oil.

25

From 5-bromopentanoic acid pentafluorophenyl ester (1.5 g, 4.32 mmol) and AgNO₃ (1.8 g, 10.80 mmol), heating to reflux and applying the same procedure described in Example 1, after flash chromatography purification (n-Hexane/EtOAc 98:2) 5-nitrooxypentanoic acid pentafluorophenyl ester (0.72 g, 50%) was obtained as a pale yellow oil.

¹H NMR (CDCl₃) δ: 4.53 (2H, t), 2.77 (2H, t), 2.00-1.85 (4H, m).

Example 4

Synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[(3-nitrooxypropyl)carbonyloxy]methyl-1H-imidazole

5 To a solution 2-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (Losartan) (2.13 g, 5.04 mmol) TEA (0.51 g, 5.04 mmol) and DMAP (0.62 g, 5.04 mmol) in DMF (25 ml) kept at 0°C, under stirring and under nitrogen atmosphere, a solution of 4-
10 nitrooxybutanoic acid pentafluorophenyl ester (1.59 g, 5.04 mmol) (Example 1) in DMF (5 ml) was added. The resulting solution was kept under stirring for further 4 hrs at room temperature. The reaction mixture was poured into a pH 3 buffer solution (50 ml), acidified with HCl 1N to pH 3-4
15 and extracted with CH₂Cl₂ (2 x 50 ml). The organic phase was washed with brine (100 ml), dried on sodium sulfate and evaporated.

After purification with Flash chromatography of the residue (CH₂Cl₂/MeOH 98:2) the title compound was obtained as a
20 white solid (1.48 g, 53%).

m.p. 66-68°C

¹H NMR (CDCl₃) δ: 7.85 (1H,d), 7.58 (2H,m), 7.42 (1H,d), 7.11 (2H,d), 6.79 (2H,d), 5.15 (2H,s), 4.94 (2H,s), 4.42 (2H,t), 2.53 (2H,t); 2.21 (2H,t), 1.93 (2H,m), 1.56 (2H,m), 1.29 (2H,
25 m), 0.85 (3H,t).

Example 5

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[(4-nitrooxybutyl)carbonyloxy]methyl-1H-
30 imidazole

Using the same procedure described in Example 4 but starting from 2-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol

(Losartan) (0.93 g, 2.19 mmol) and 5-nitrooxypentanoic acid pentafluorophenyl ester (Example 3) (0.72 g, 2.19 mmol) after purification with Flash chromatography of the residue (CH₂Cl₂/MeOH 98:2) the title compound (0.72 g, 60%) was
5 obtained as a white foam.

¹H NMR (CDCl₃) δ: (CDCl₃): 7.72-7.48 (4H, m); 7.10 (2H, d); 6.94 (2H, d); 5.24 (2H, s); 5.00 (2H, s); 4.44 (2H, t); 2.10 (2H, t); 1.57-1.44 (6H, m); 1.29 (4H, m); 0.33 (3H, t).

10

Example 6

Synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[(4-(nitrooxymethyl)phenylcarbonyloxymethyl-1H-imidazole; Losartan 4-(nitrooxymethyl)benzoic acid ester

15

To a solution of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (Losartan) (3.1 g, 7.27 mmol) Sc(OTf)₃ (0.3 g, 0.61 mmol) and DMAP (1.5 g, 12.12 mmol) in CH₂Cl₂ (25 ml) kept at -5°C, under stirring and under nitrogen atmosphere, a
20 solution of 4-(nitrooxymethyl)benzoic acid pentafluorophenyl ester (Example 2) (2.2 g, 6.06 mmol) in CH₂Cl₂ (5 ml) was added. The resulting solution was kept under stirring for further 16 hrs at room temperature. The reaction mixture was poured into a pH 3 buffer solution (50 ml), acidified
25 with HCl 1 N to pH 3-4 and extracted with CH₂Cl₂ (2 x 50 ml). The organic phase was dried on sodium sulfate and evaporated.

30

After purification with Flash chromatography of the residue (CH₂Cl₂/MeOH 98:2) the title compound was obtained as a white solid (1.70 g, 47%).

m.p. 155°C

¹H NMR (DMSO) δ: 7.73-7.56 (7H, m), 7.24 (1H, d), 7.00 (4H, m), 5.60 (2H, s), 5.39 (2H, s), 5.28 (2H, s), 2.61 (2H, t), 1.53 (2H, m), 1.28 (2H, m), 0.82 (3H, t)

5

Example 7

Synthesis of 2-butyl-4-chloro-1-[[2'-(1-(3-nitrooxypropyl carbonyl)-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[(3-nitrooxypropyl)carbonyloxy]methyl-1H-imidazole (Compound 433)

10 To a solution of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[(3-nitrooxypropyl) carbonyloxy]methyl-1H-imidazole (Example 4) (0.5 g, 0.9 mmol), TEA (0.125 ml 0.9 mmol), DMAP (0.11 g, 0.9 mmol) in CH₂Cl₂, cooled to 0 °C, a solution of 4-nitrooxybutanoic
15 acid pentafluorophenyl ester (Example 1) (0.28 g, 0.9 mmol) in CH₂Cl₂ (1 ml) was added. After 8 hrs at room temperature the reaction was refluxed for 4 hrs. Then was cooled, diluted with water, the two phases were separated and the organic phase was washed first with pH 3 buffer solution
20 then with brine, dried and evaporated.

After Flash chromatography purification (n-Hexane/EtOAc 9:1) the title compound (0.053 g, 10%) was isolated as a white foam.

1H NMR (CDCl₃) δ: 7.87-7.42 (4H, m); 7.13 (2H, d); 6.81 (2H, d);
25 5.15 (2H, s); 4.92 (2H, s); 4.42 (4H, m); 2.53-2.40 (4H, m); 2.21 (2H, t); 1.87-1.56 (6H, m); 1.29 (2H, m); 0.85 (3H, t).

Example 8

Synthesis of 2-Butyl-4-chloro-1-[[2'-(1-(3-nitrooxypropyl carbonyl)-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-
30 imidazole-5-carboxaldehyde (Compound 382)

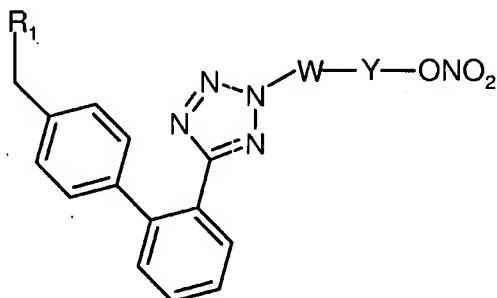
Following the same procedure described in Example 7 but starting from 2-butyl-4-chloro-1-[[2'-(1H)-tetrazol-5-

yl)[1,1'-biphenyl]-4-yl)methyl]-1H-imidazole-5-carboxaldehyde (0.38 g, 0.9 mmol) and 4-nitrooxybutanoic acid pentafluorophenyl ester (Example 1) (0.28 g, 0.9 mmol) the title compound (0.54 g, 12 %) was obtained as a white
5 foam.

¹H NMR (DMSO) δ: 9.61(1H,s); 7.70-7.62(2H,m); 7.56-7.50(2H,m); 7.12(2H,d); 6.81(2H,d); 5.57(2H,s); 4.45(2H,t); 2.55-2.40(4H,m); 1.81-1.51(4H,m); 1.27(2H,m); 0.83(3H,t).

Claims

1. Compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

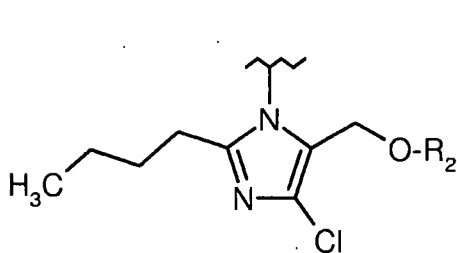


5

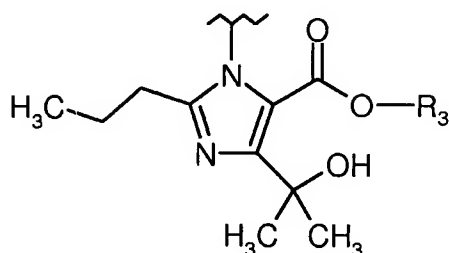
(I)

wherein:

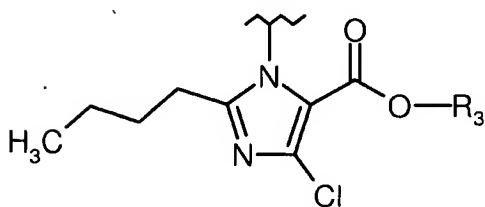
R₁ is selected from the group consisting of:



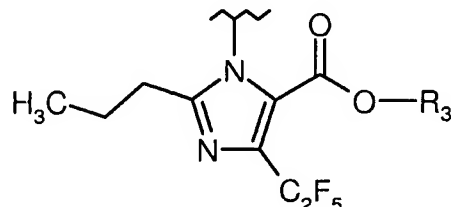
(Ia)



(Ib)

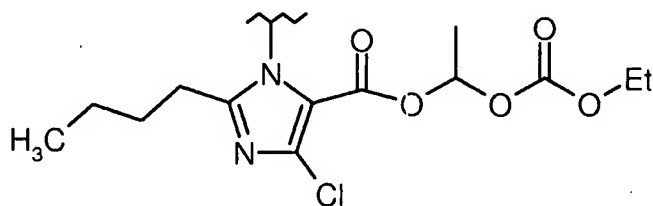


(Ic)

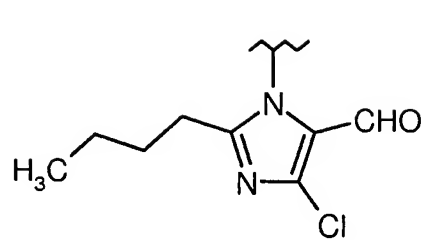


(Id)

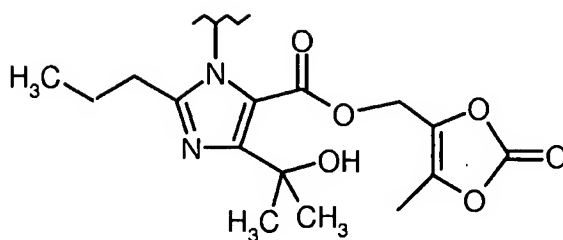
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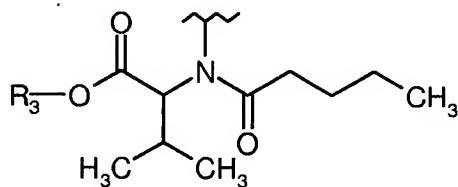
(Ie)



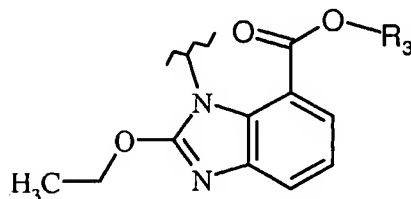
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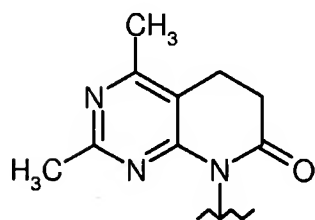
(Ig)



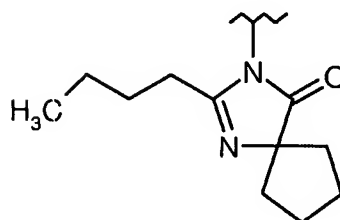
(Ih)



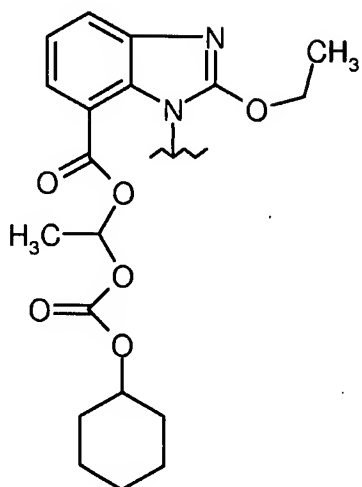
(Ii)



(Il)



(Im)



(In)

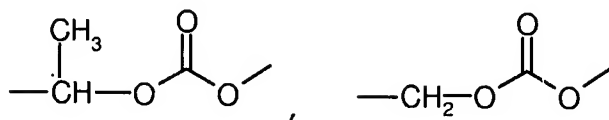
wherein

10 R_2 is H, or $-W_1-Y_0-ONO_2$ wherein W_1 is
 $-C(O)-$ or $-C(O)O-$;

Y_0 is as reported below;

R₃ is H, -Y₀-ONO₂ or -W₂-Y₀-ONO₂, wherein

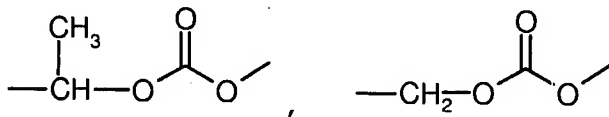
W₂ is



Y₀ is as reported below;

5 W has the following meanings:

-C(O)-, -C(O)O-,



Y and Y₀ are the same or different and are bivalent radicals having the following meanings:

10 a)

- straight or branched C₁-C₂₀ alkylene, preferably C₁-C₁₀ alkylene, more preferably C₃-C₆ alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, -ONO₂

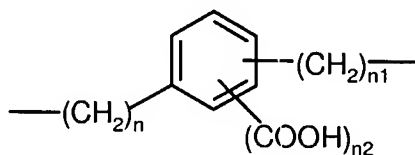
15 or T₀, wherein T₀ is

-OC(O)-(C₁-C₁₀ alkyl)-ONO₂ or -O-(C₁-C₁₀ alkyl)-ONO₂;

- cycloalkylene having from 5 to 7 carbon atoms, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon

20 atoms, preferably T is CH₃;

b)



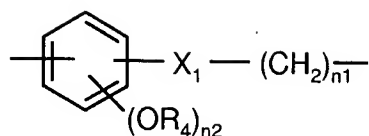
wherein

n is an integer from 0 to 20,

25 n₁ is an integer from 1 to 20,

n₂ is 0 or 1;

c)



wherein:

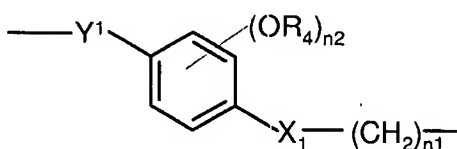
$n1$ is an integer from 1 to 20,

$n2$ is 0 or 1;

5 X_1 is $-(CH_2)_3-OC(O)-$ or $-CH=CH-C(O)O-$, and

R_4 is H or CH_3 ;

d)



wherein:

10 $n1$ is an integer from 1 to 20,

$n2$ is 0 or 1;

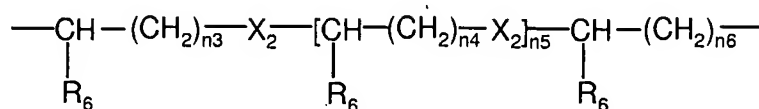
Y^1 is $-CH=CH-$, $-(CH_2)_3-$,

X_1 is $-OC(O)-$, $-C(O)O-$, and

R_4 is H or CH_3 ,

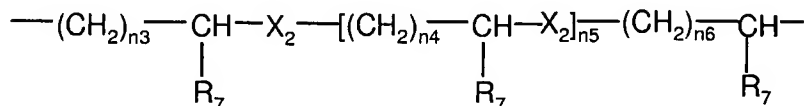
15 when Y or Y_0 are selected from the bivalent radicals of the groups b), c) or d) the $-ONO_2$ group is linked to $-(CH_2)_{n1}$ -group;

g)



20

h)

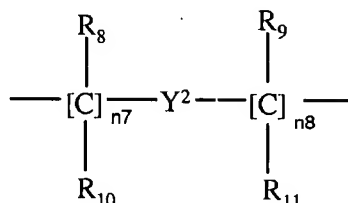


wherein X_2 is O or S,

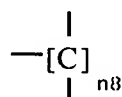
$n3$, $n4$ and $n6$ are integer independently selected from 0 to

25 20,

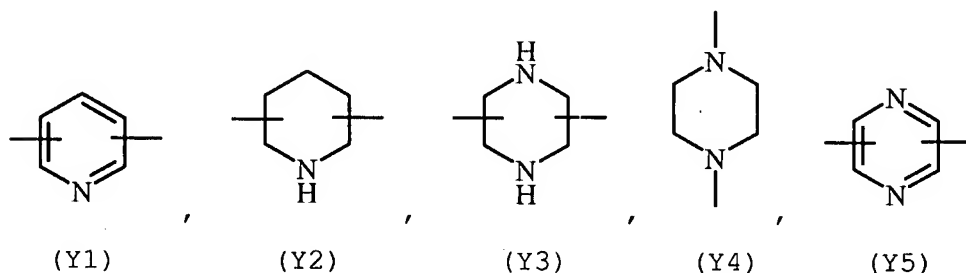
- n5 is an integer from 0 to 6,
 R₆ is H, CH₃ or a nitrooxy group,
 R₇ is CH₃ or a nitrooxy group;
 when Y or Y₀ are selected from the bivalent radicals of the
 5 group g) the -ONO₂ group is linked to -(CH₂)_{n6}- group;
 when Y or Y₀ are selected from the bivalent radicals of the
 group h) the -ONO₂ group is linked to -CH(R₇)- group;
 i)

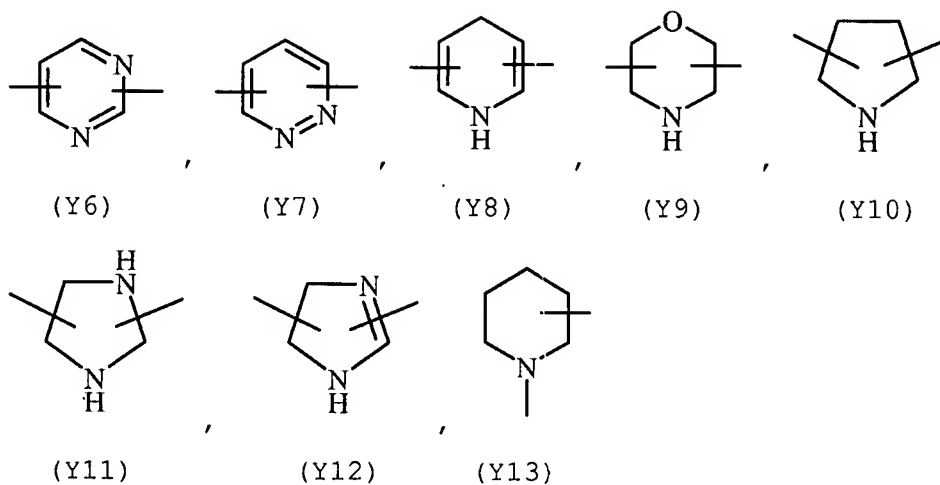


- 10 wherein:
 n7 is an integer from 0 to 10;
 n8 is an integer from 1 to 10;
 R₈ R₉, R₁₀, R₁₁ are the same or different, and are H or
 straight or branched C₁-C₄ alkyl, preferably R₈ R₉, R₁₀, R₁₁
 15 are H;
 wherein the -ONO₂ group is linked to



- wherein n8 is as defined above;
 Y² is an heterocyclic saturated, unsaturated or aromatic 5
 20 or 6 members ring, containing one or more heteroatoms
 selected from nitrogen, oxygen, sulfur,
 and is selected from



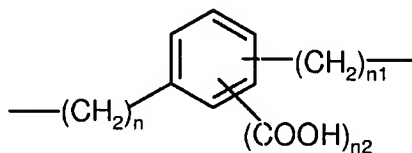


5

2. Compounds of formula (I) according to claim 1 wherein Y and Y₀ equal or different are selected from

- a) straight or branched C₁-C₁₀ alkylene,
b)

10



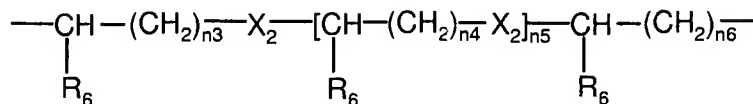
wherein

n is 0 or 1,

n₁ is 1,

n₂ is 0;

15 g)



wherein

X₂ is 0 or S,

20 n₃ and n₆ are selected from 1 to 5,

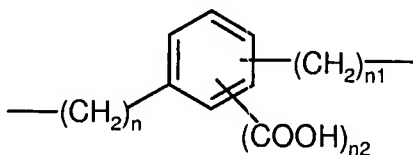
n₅ is 0,

R₆ is H.

3. Compounds of formula (I) according to claim 1 wherein R_1 is a radical of formula (Ia), (Ib), (Ic), (Id), (Ih) or (Ii) wherein R_2 and R_3 are H.

5 4. Compounds of formula (I) according to claims 3 wherein Y is

- a) straight or branched C_1 - C_{10} alkylene,
b)



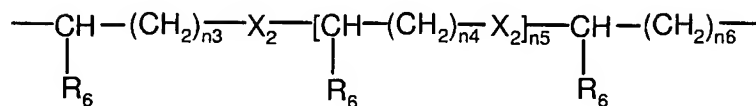
10 wherein

n is 0 or 1,

$n1$ is 1,

$n2$ is 0;

g)



15

wherein

X_2 is 0 or S,

$n3$ and $n6$ are selected from 1 to 5,

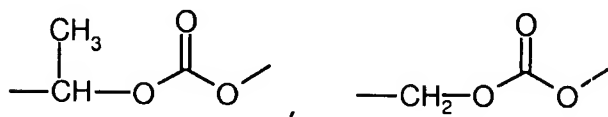
20 $n5$ is 0,

R_6 is H.

5. Compounds of formula (I) according to claim 1 wherein R_1 is (Ia) wherein

25 R_2 is $-W_1-Y_0-ONO_2$, W_1 is $-C(O)-$,

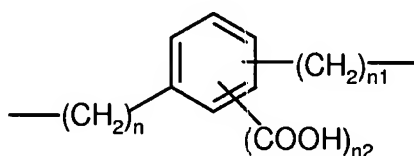
W is



6. Compounds of formula (I) according to claim 1 wherein
 R_1 is (Ia) wherein
 R_2 is $-W_1-Y_0-ONO_2$ wherein W_1 is $-C(O)-$ or $-C(O)O-$,
 W is $-C(O)-$, $-C(O)O-$.

5

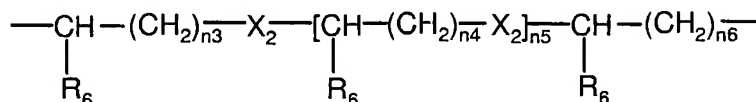
7. Compounds of formula (I) according to claims 5 and 6
 wherein Y and Y_0 equal or different are
 a) straight or branched C_1-C_{10} alkylene,
 b)



10

wherein
 n is 0 or 1,
 $n1$ is 1,
 $n2$ is 0;

15 g)



wherein

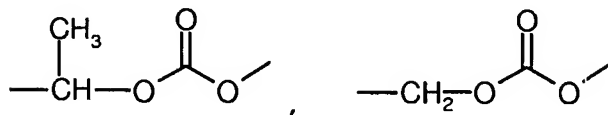
X_2 is O or S,

20 $n3$ and $n6$ are selected from 1 to 5,

$n5$ is 0,

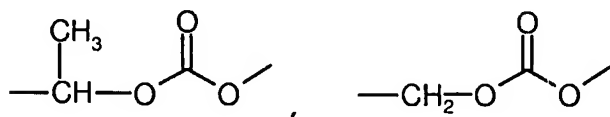
R_6 is H.

8. Compounds of formula (I) according to claim 1 wherein
 R_1 is a radical of formula (Ib), (Ic), (Id), (Ih) or (Ii),
 wherein R_3 is $-Y_0-ONO_2$, and
 W is



9. Compounds of formula (I) according to claim 1 wherein R_1 is a radical of formula (Ib), (Ic), (Id), (Ih) or (Ii) wherein R_3 is $-Y_0-ONO_2$, and W $-C(O)O-$

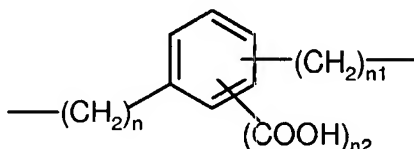
5 10. Compounds of formula (I) according to claim 1 wherein R_1 is a radical of formula (Ib), (Ic), (Id), (Ih) or (Ii) wherein R_3 is $-W_2-Y_0-ONO_2$, and W_2 and W are



10

11. Compounds of formula (I) according to claims 8 to 10 wherein Y and Y_0 equal or different are

- a) straight or branched C_1-C_{10} alkylene,
- b)



15

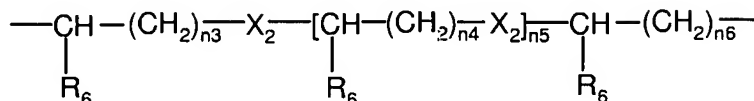
wherein

n is 0 or 1,

$n1$ is 1,

$n2$ is 0;

20 g)



wherein

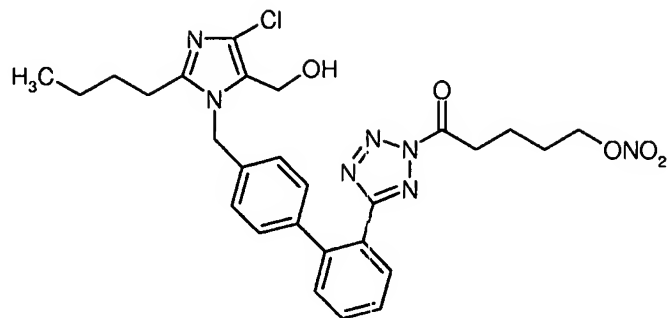
X_2 is O or S,

25 $n3$ and $n6$ are selected from 1 to 5,

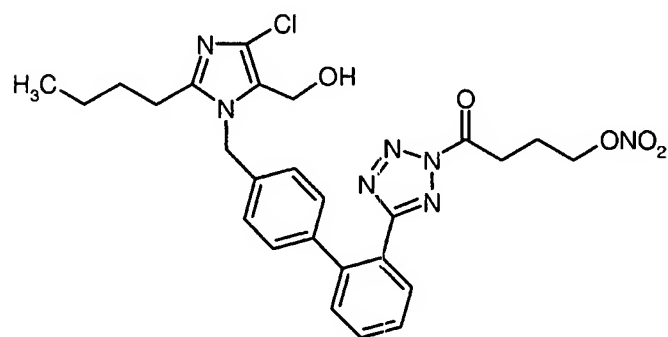
$n5$ is 0,

R_6 is H.

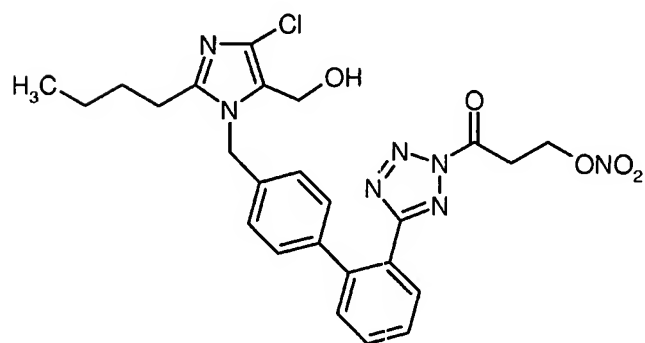
12. Compound of formula (I) according to claims 1 to 4 selected from:



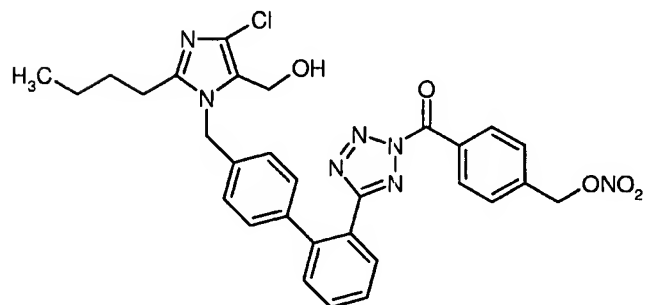
(1)



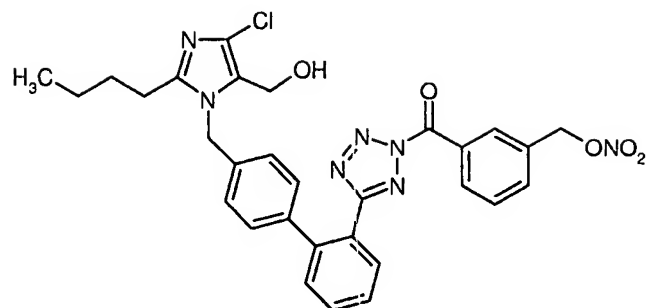
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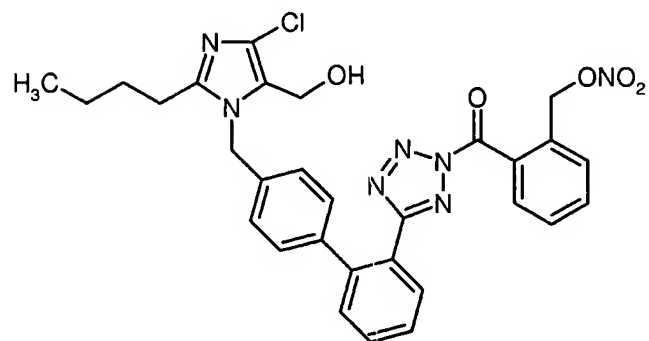
(3)



(4)

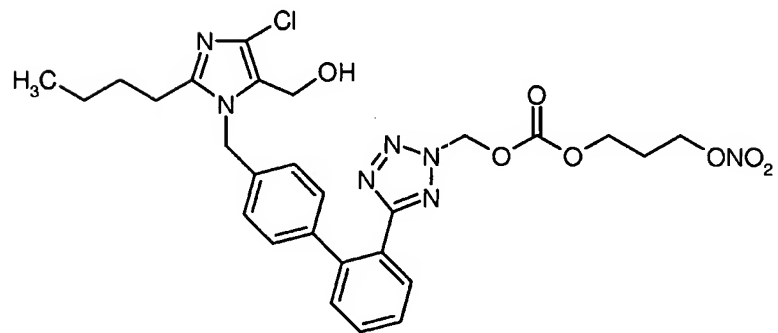


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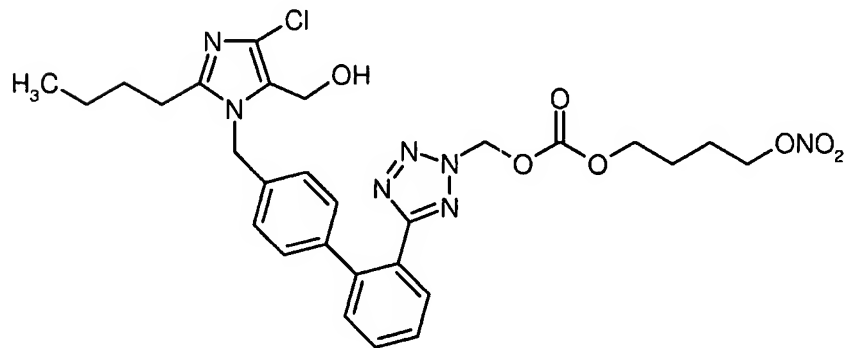


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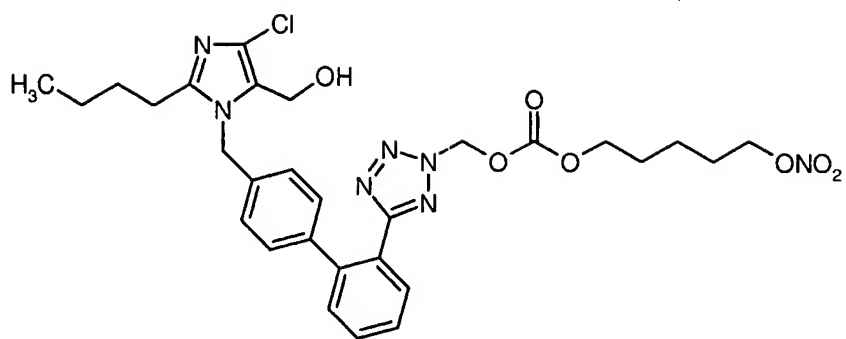
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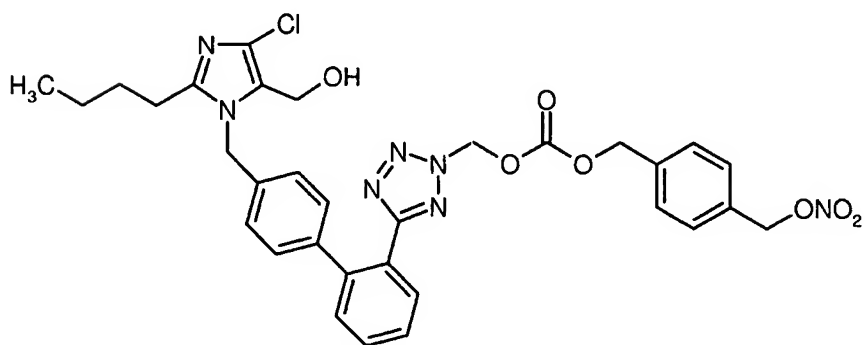
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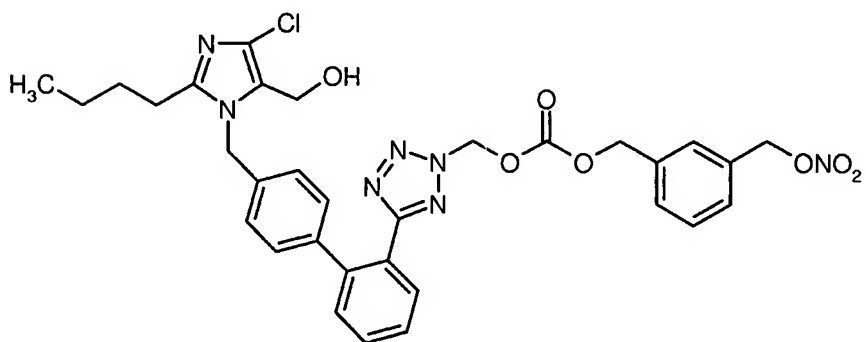
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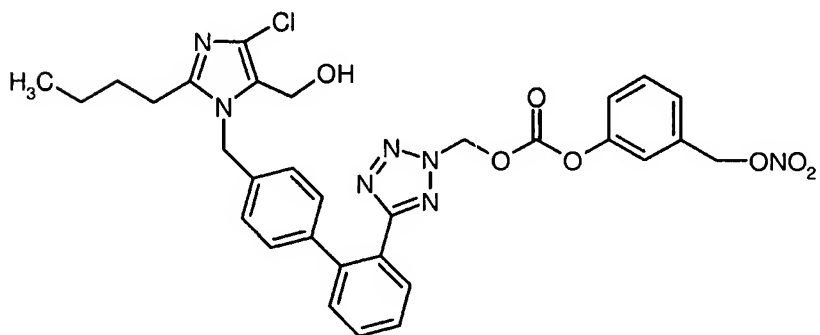
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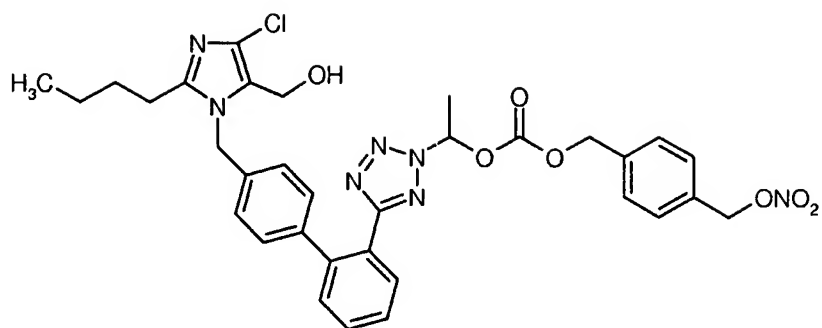
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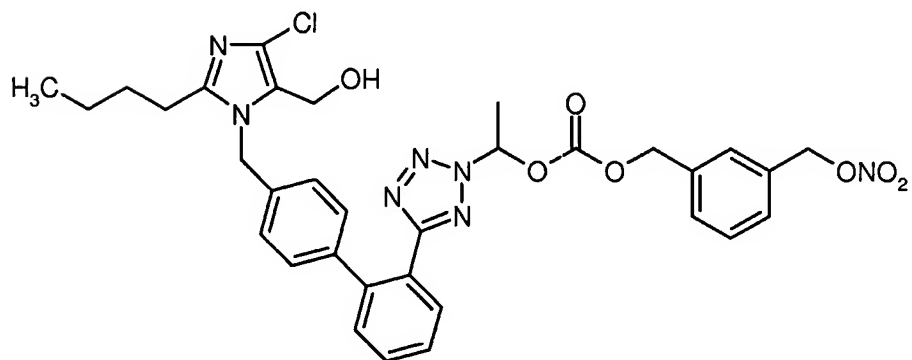
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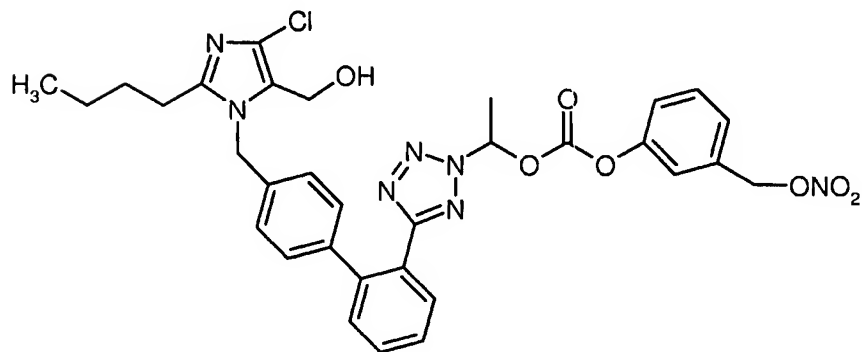
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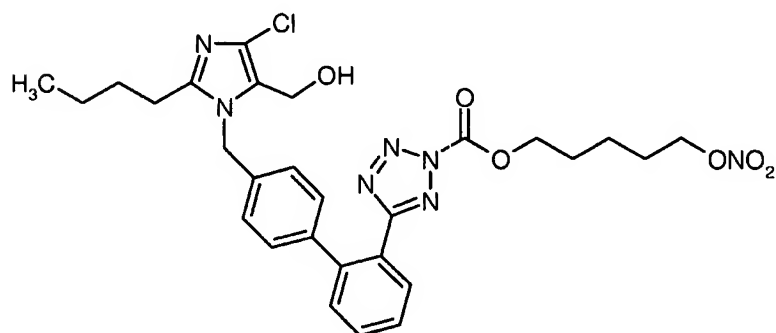
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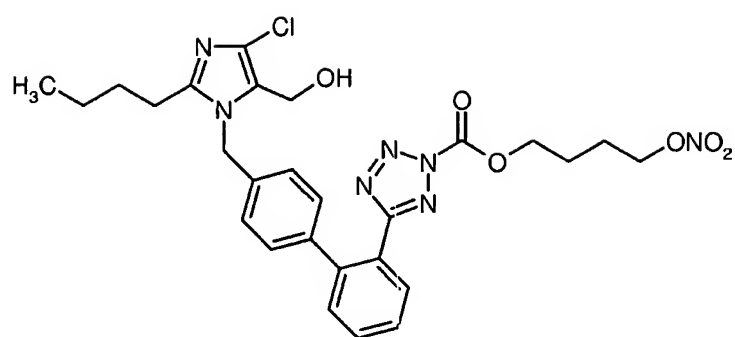
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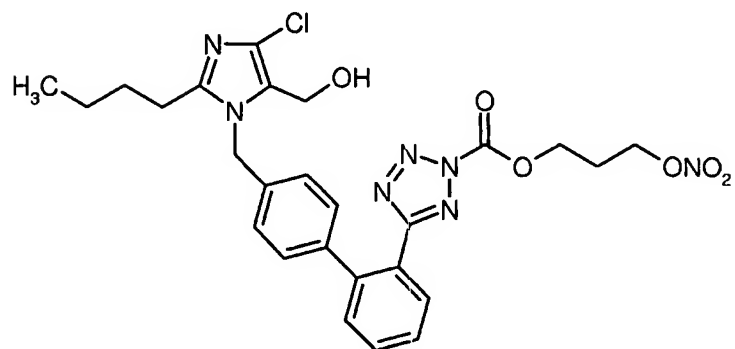
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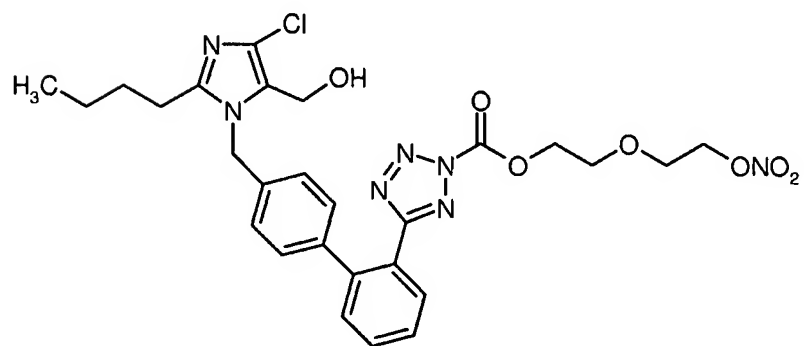
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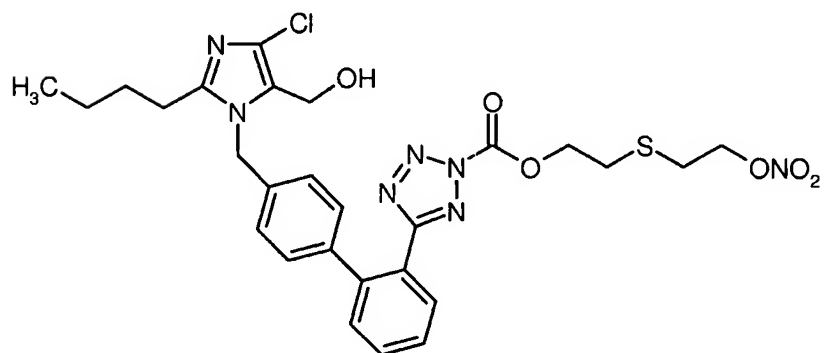
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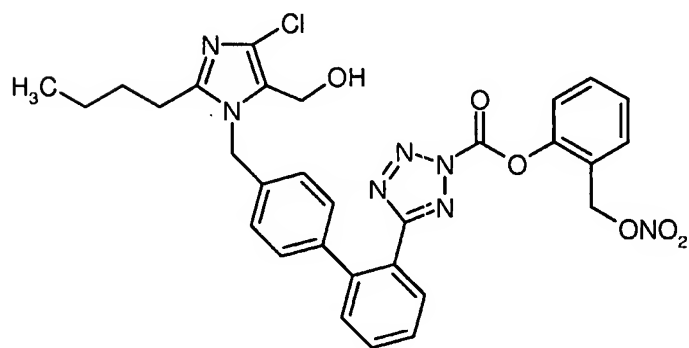
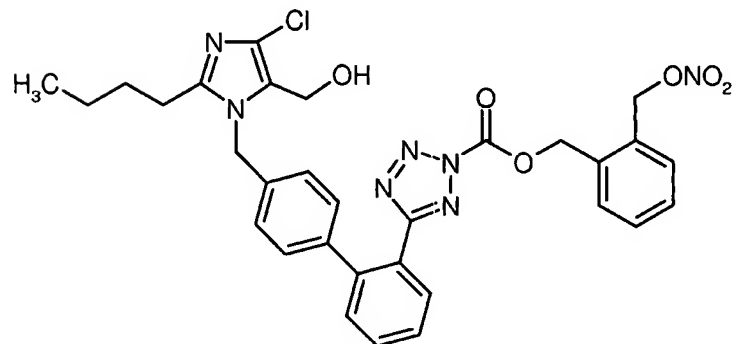
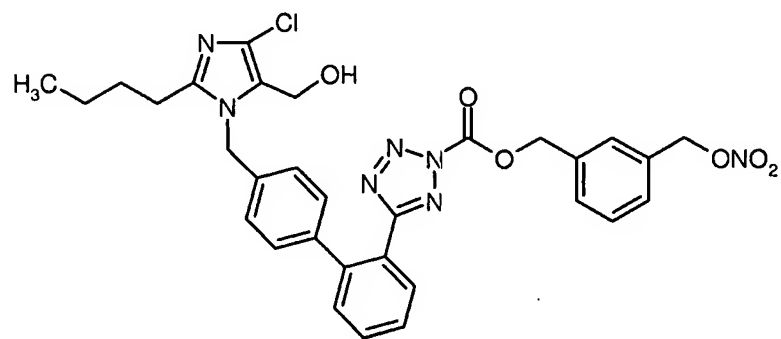
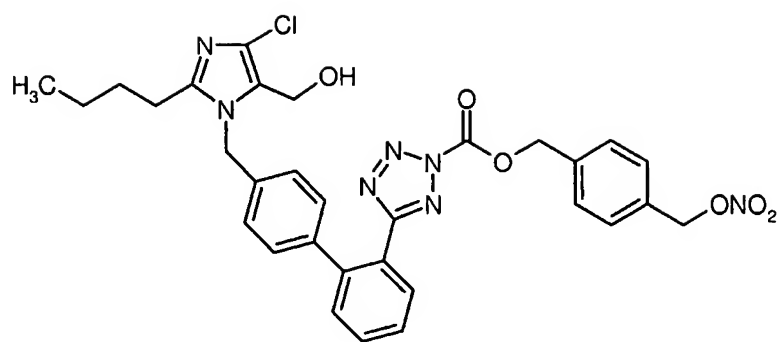
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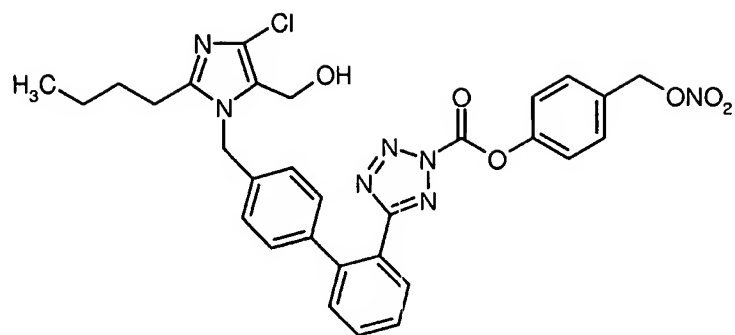


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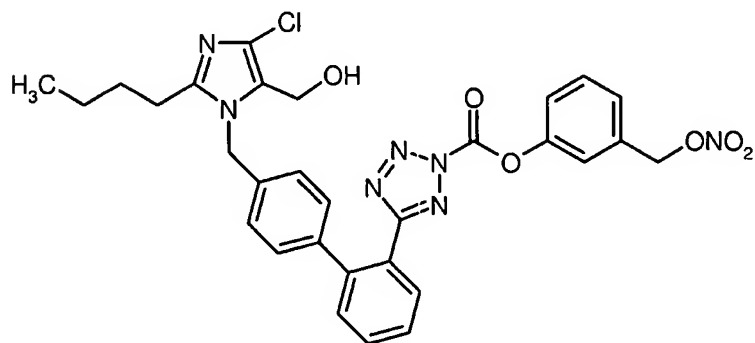


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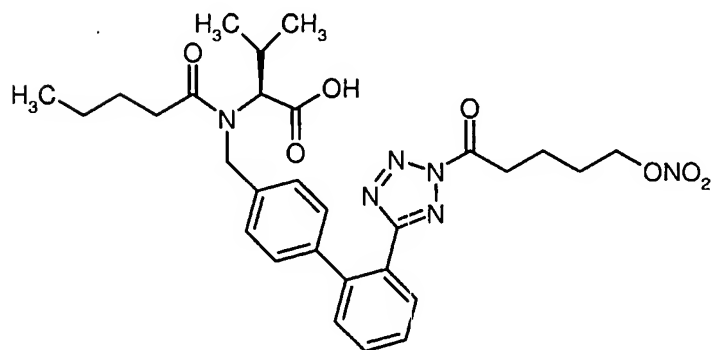




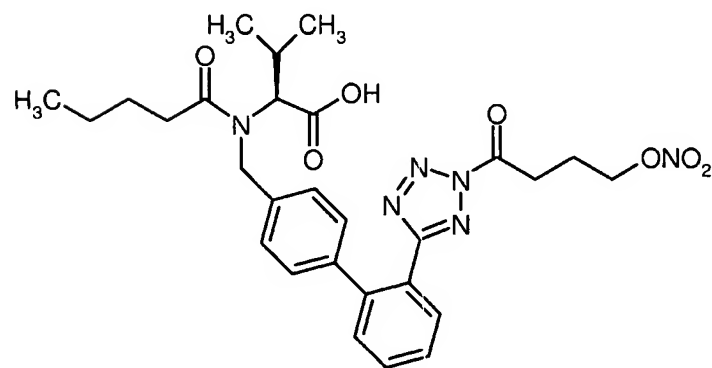
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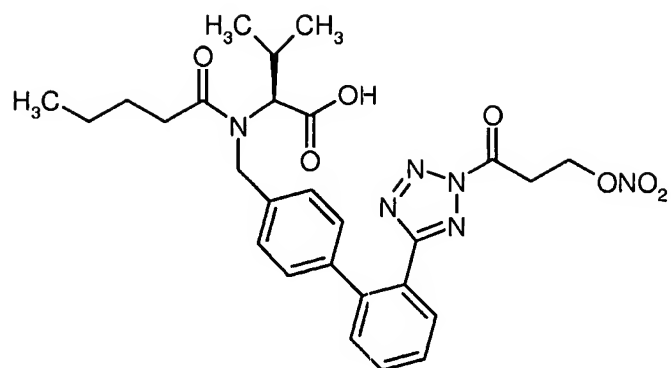
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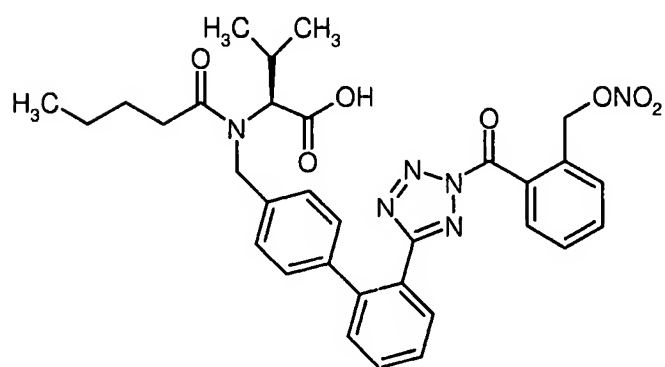
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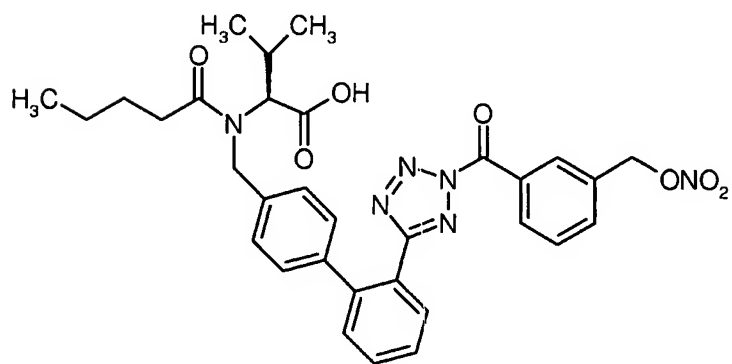
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(29)

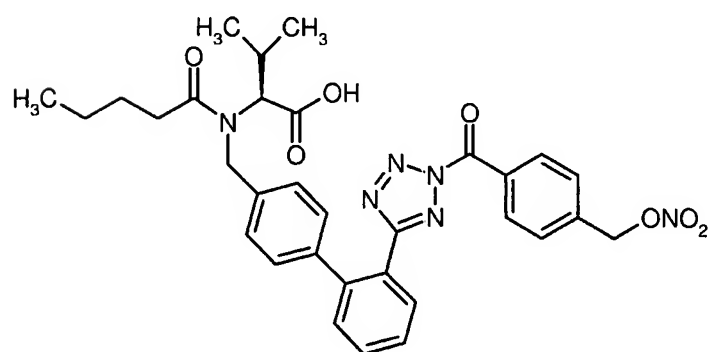


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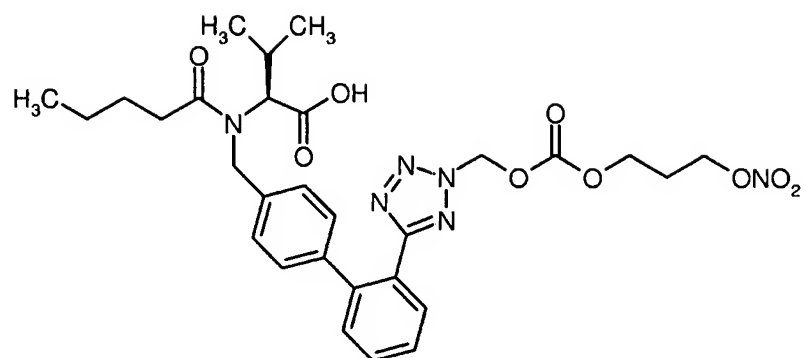
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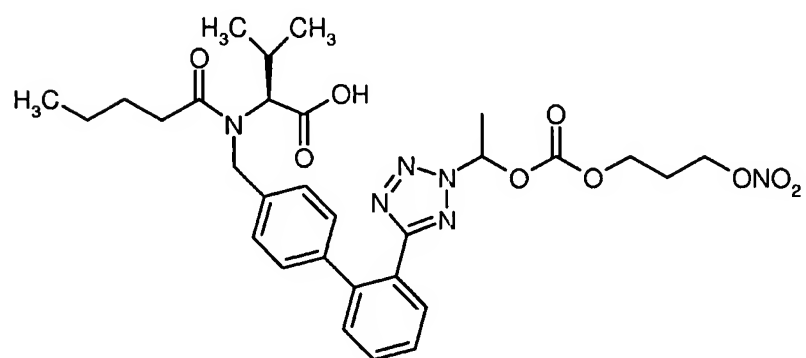


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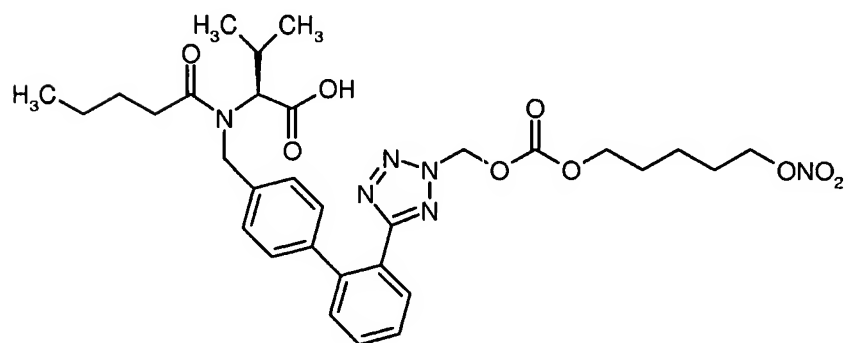
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(33)

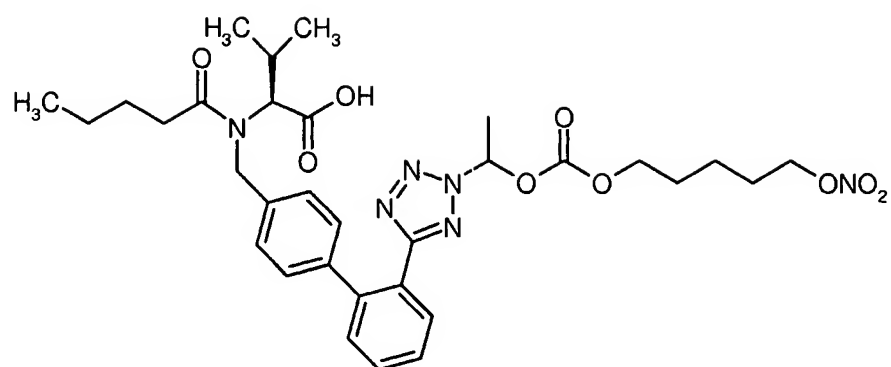


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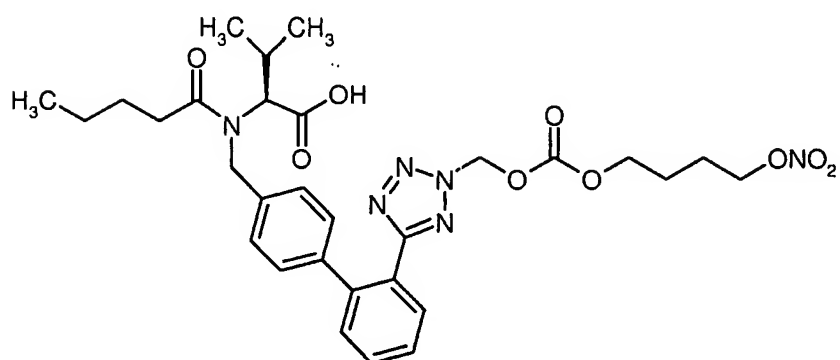


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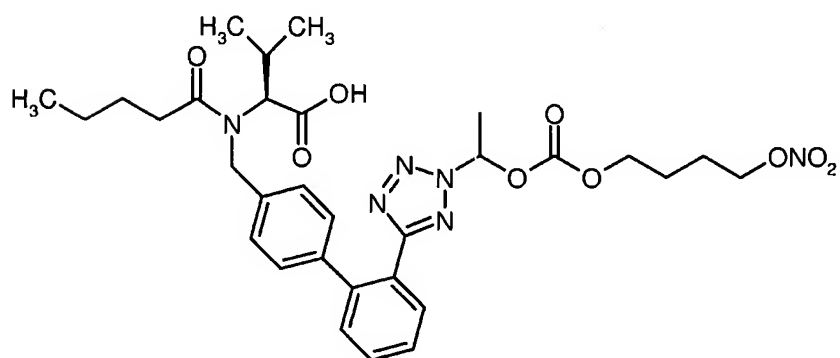
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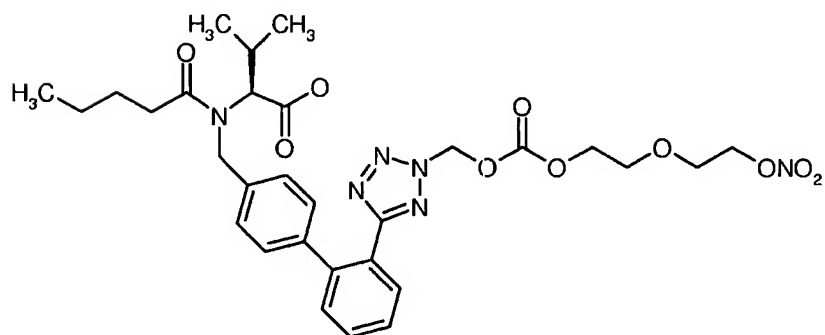
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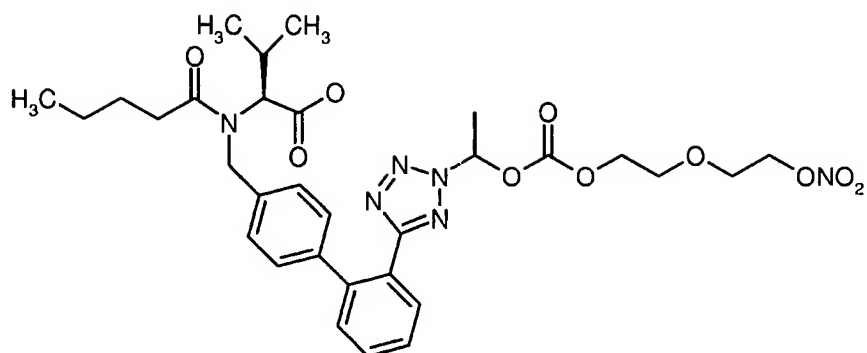
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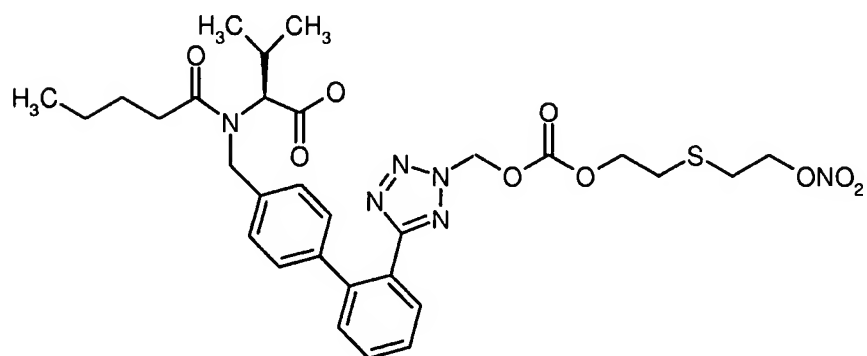
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(39)

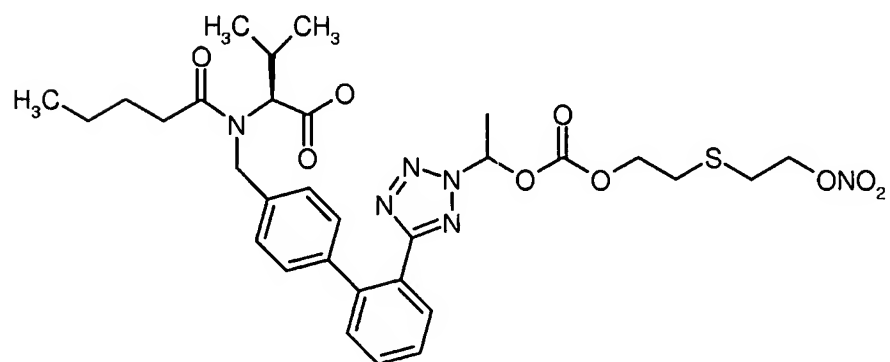


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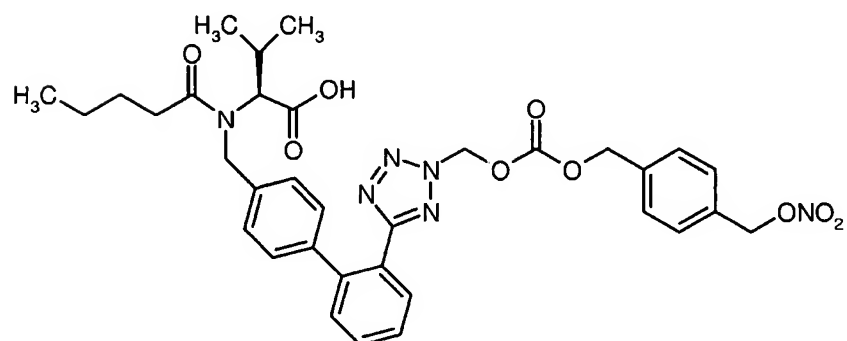


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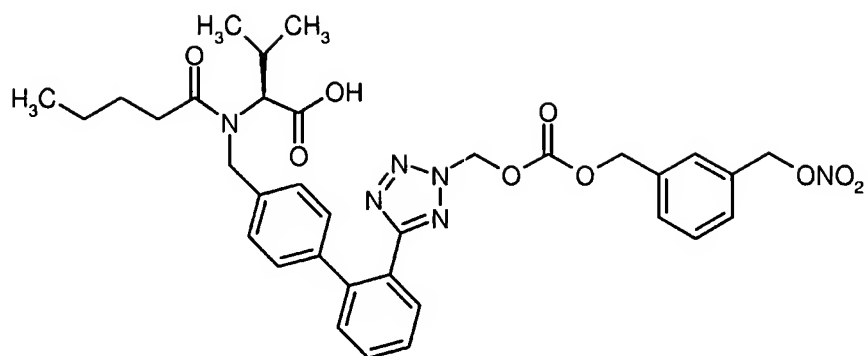


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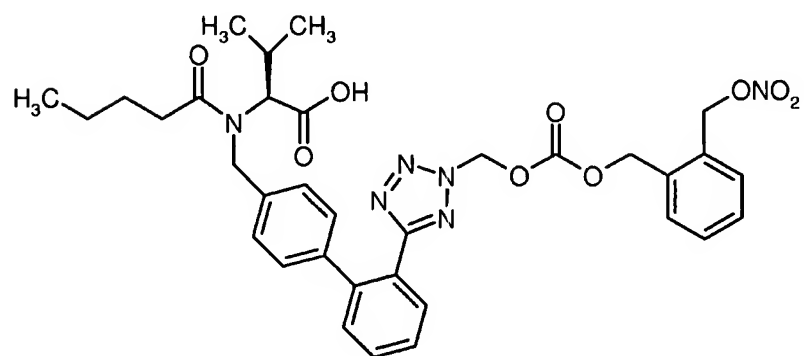


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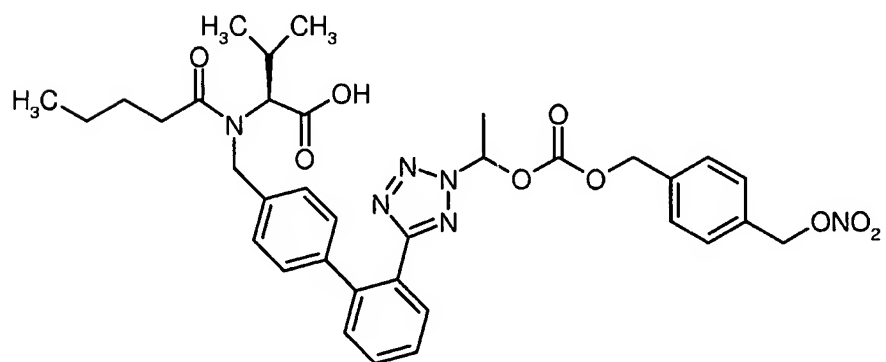
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(44)

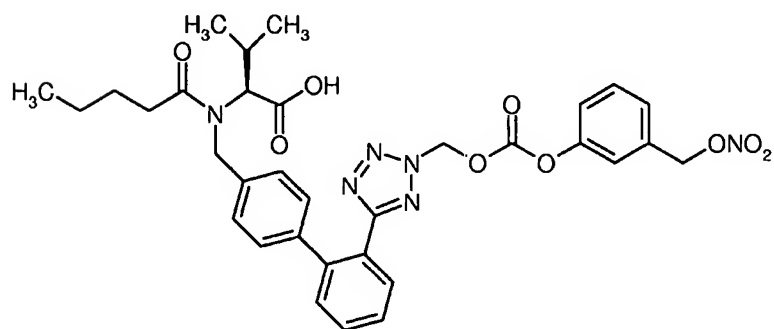
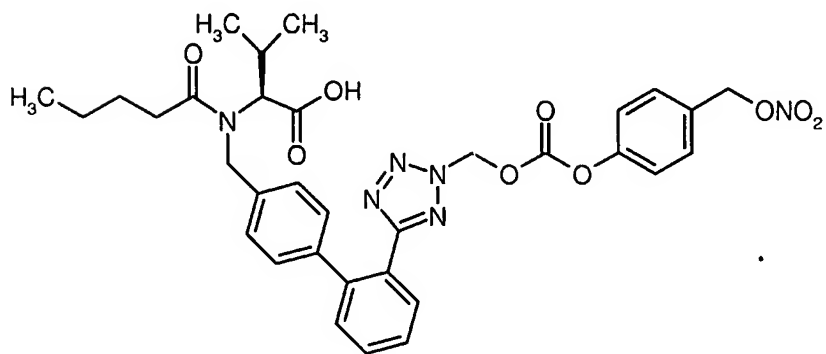
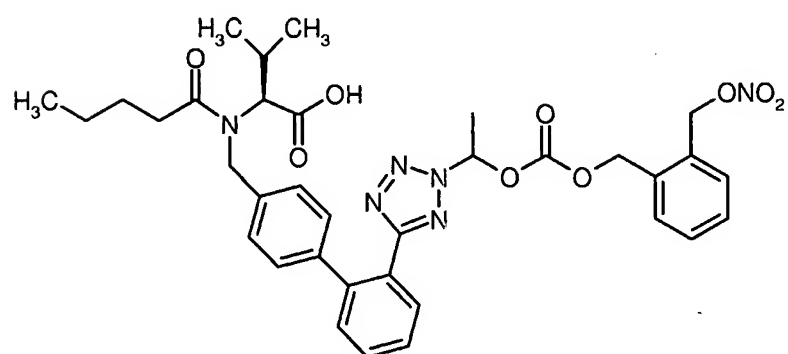
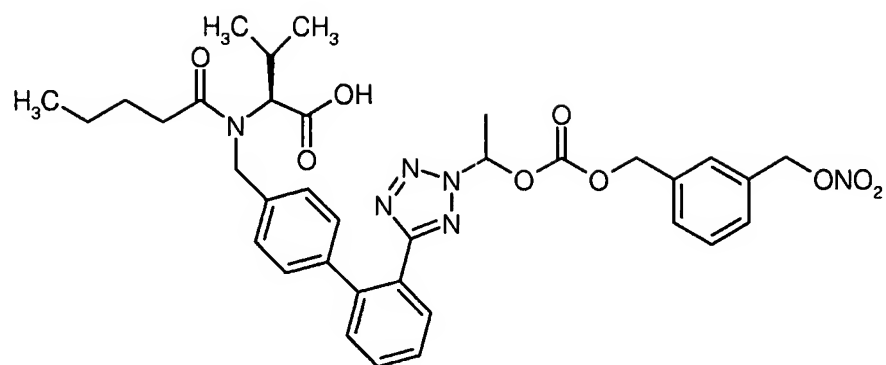


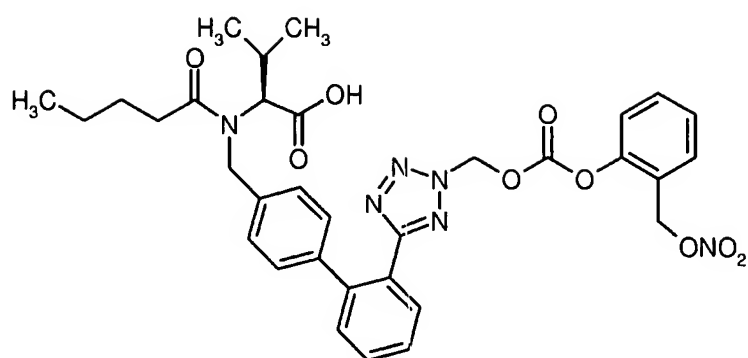
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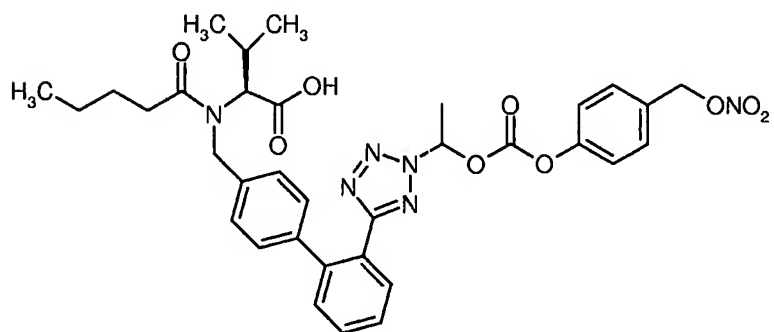
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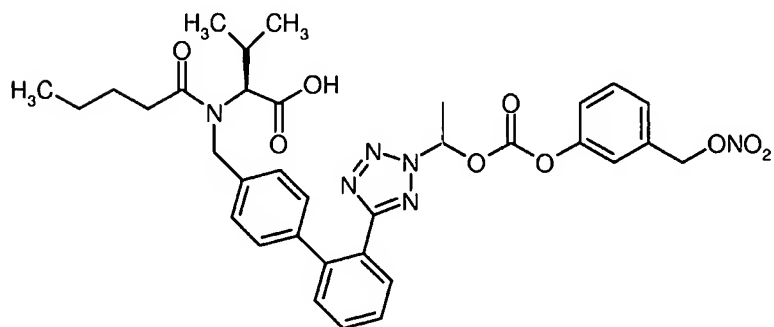




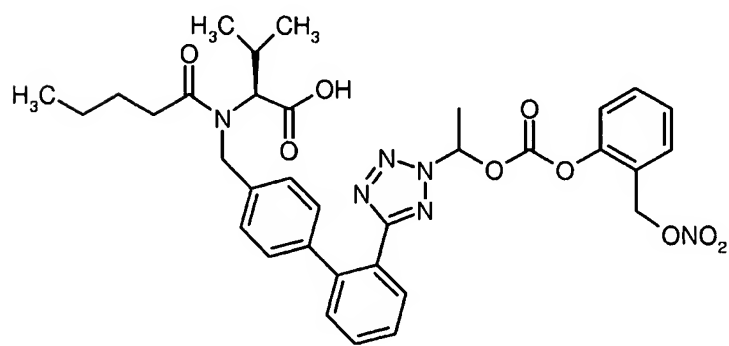
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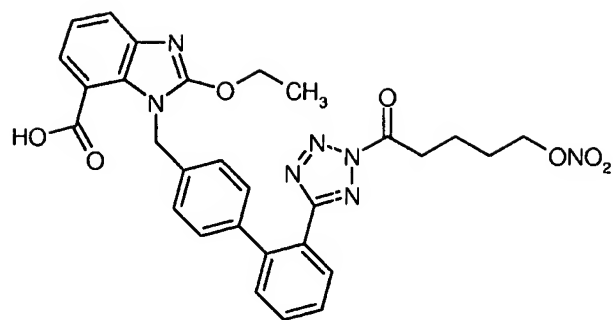
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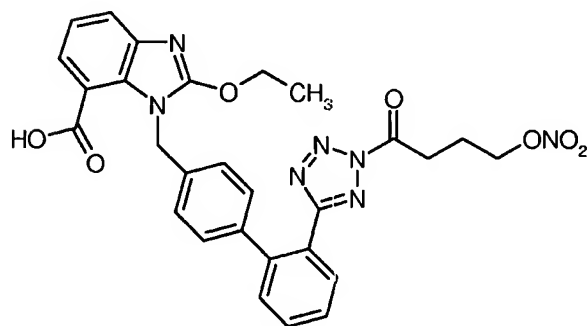
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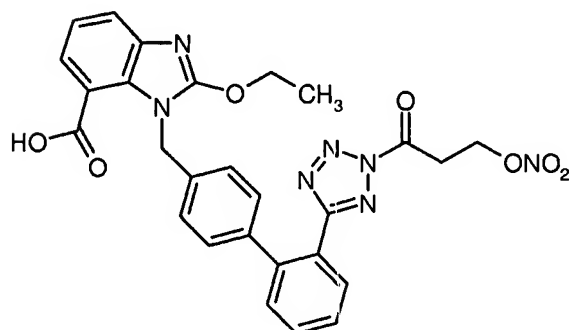
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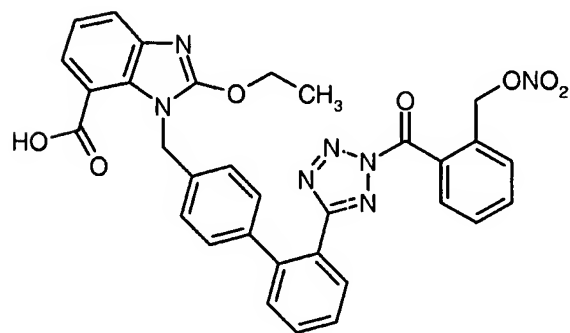
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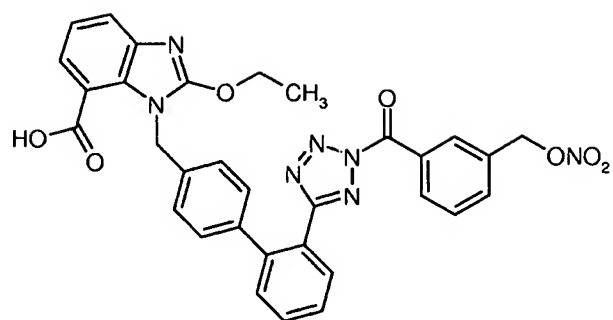
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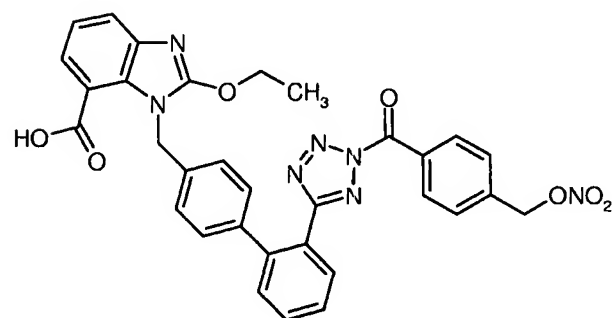
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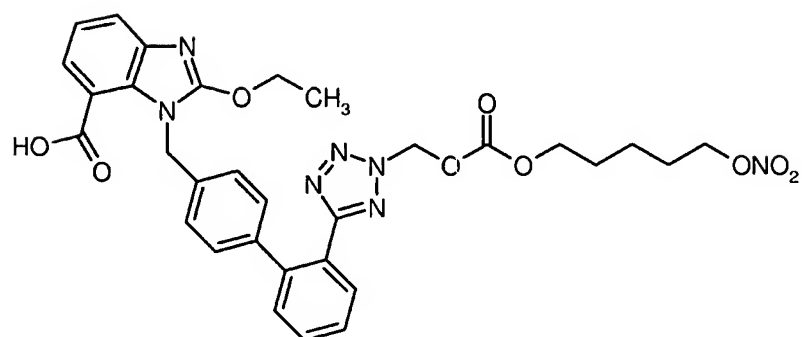
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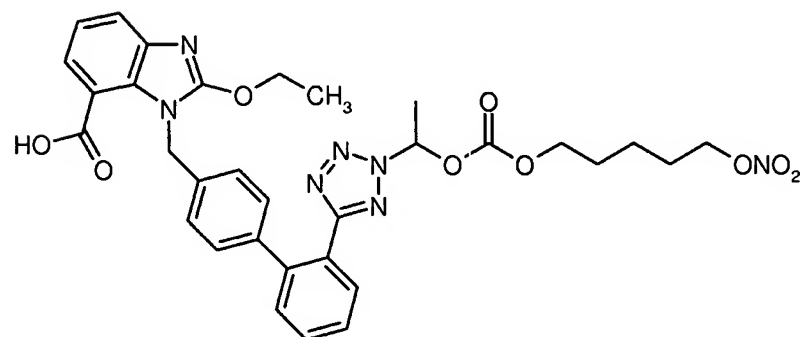
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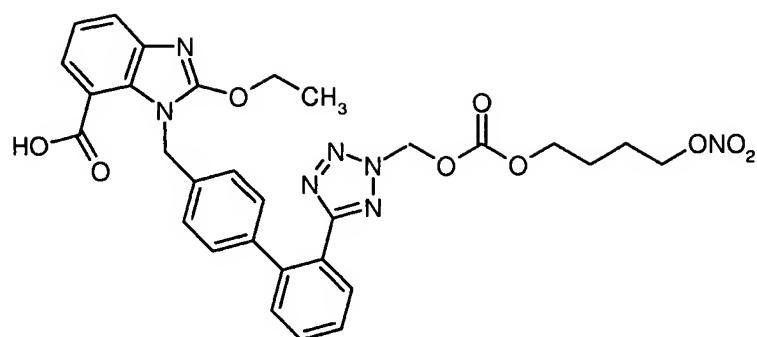
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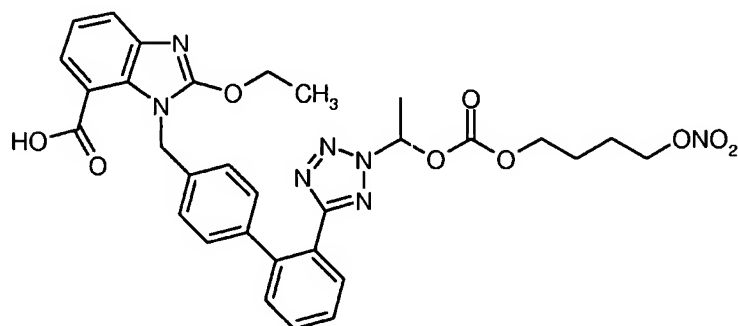
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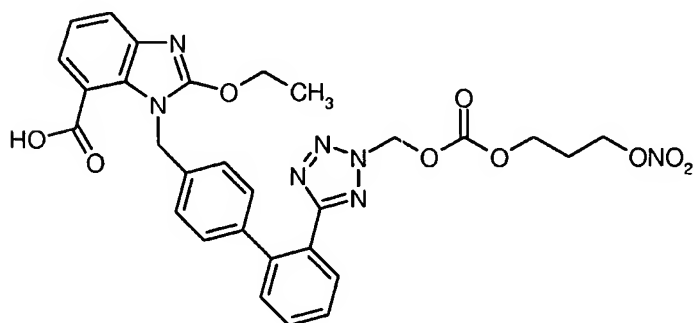
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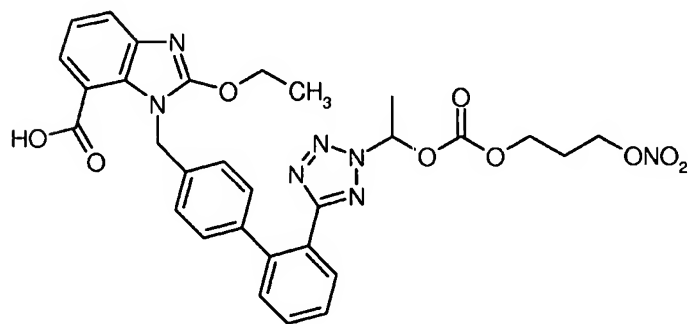
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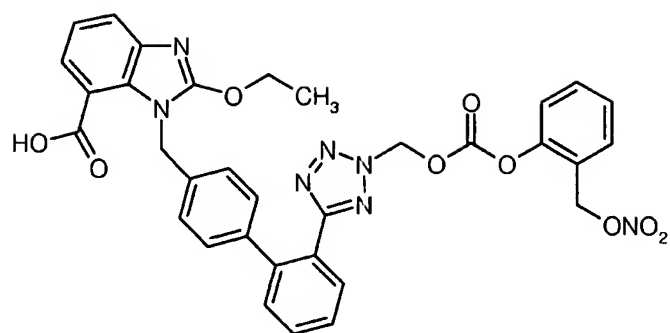
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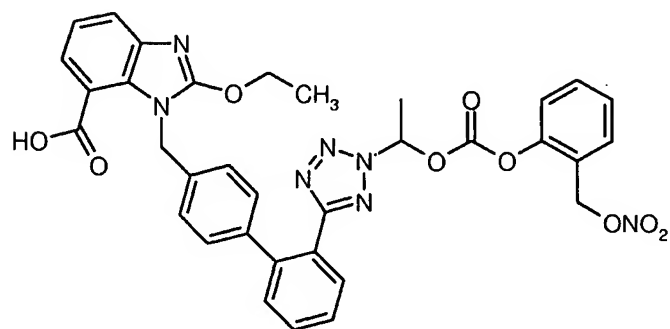
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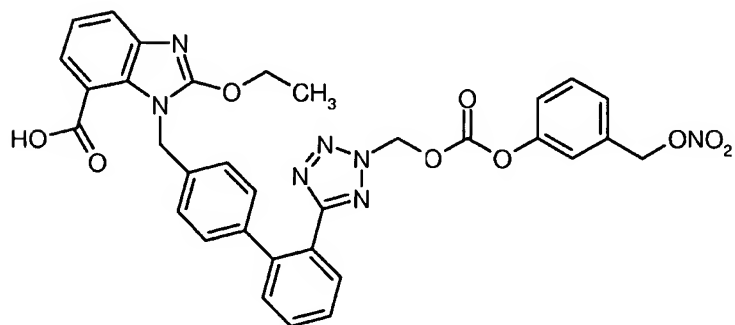
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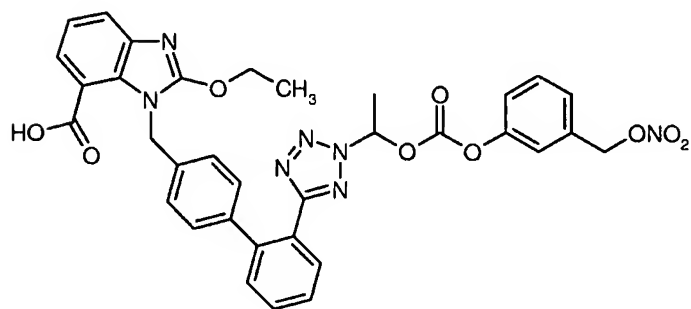
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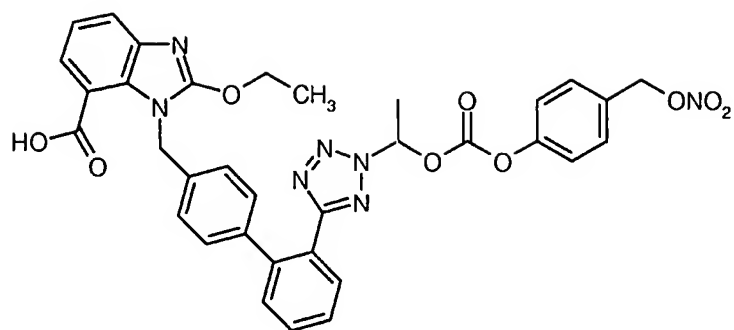
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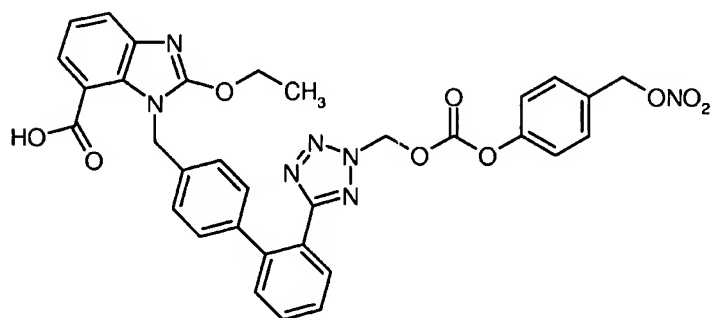
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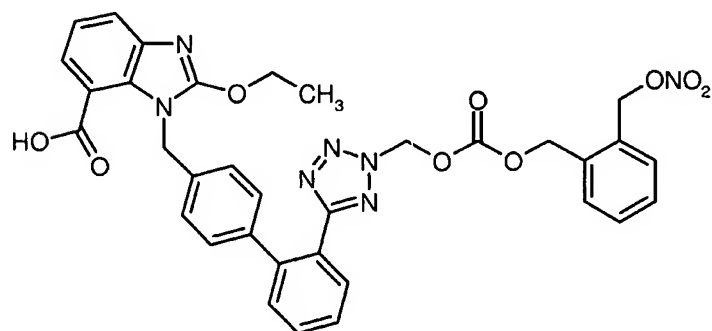
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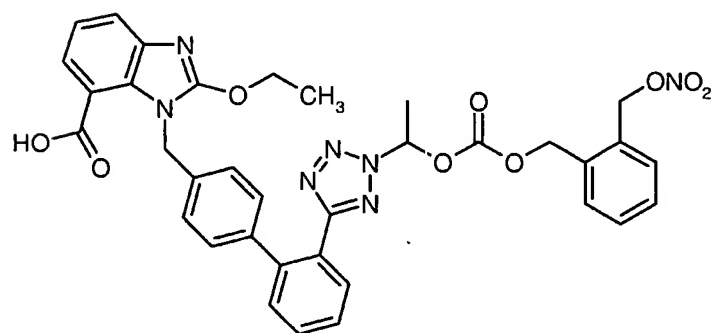
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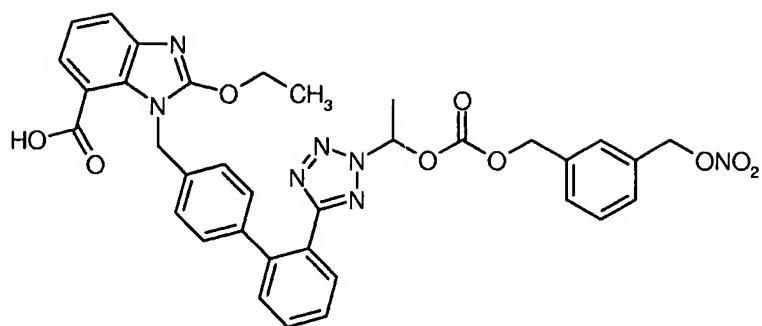
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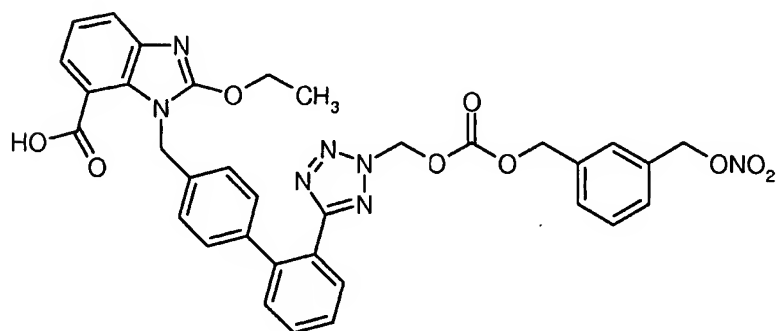
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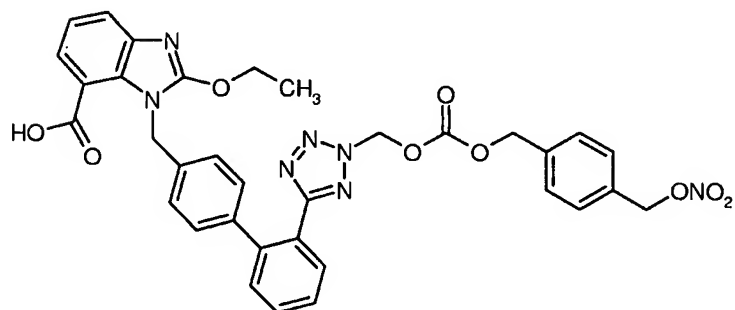
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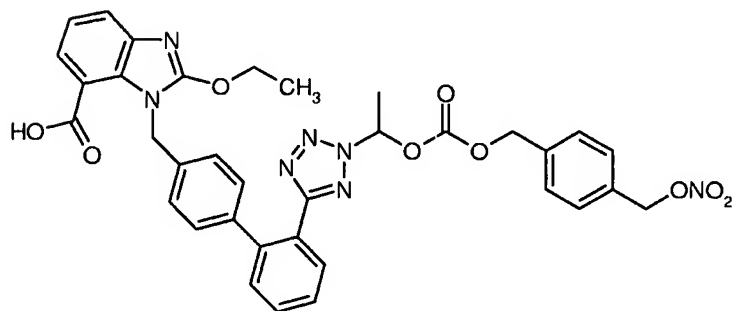
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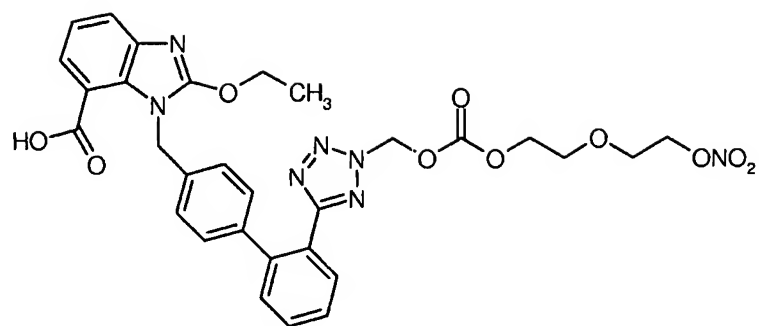
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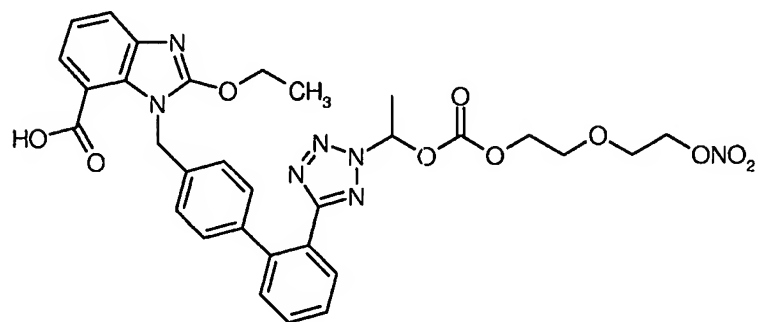
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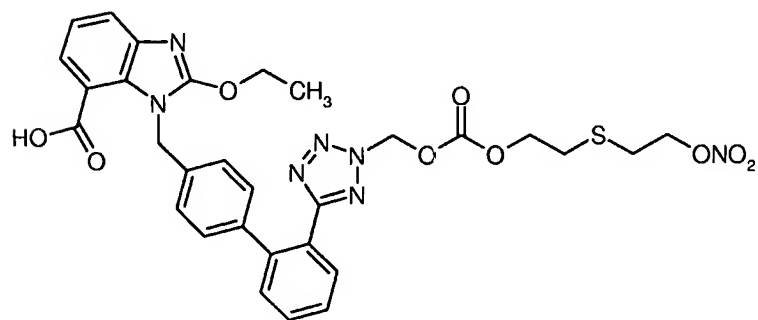
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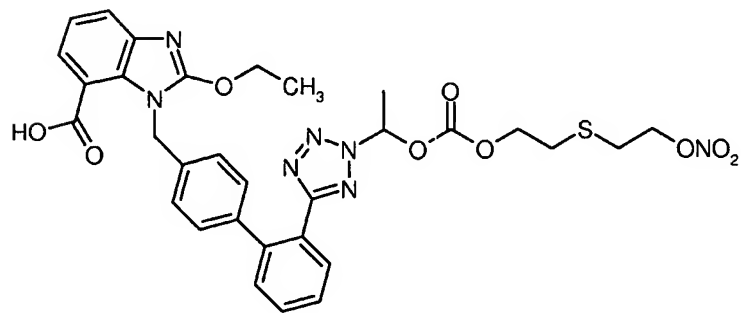
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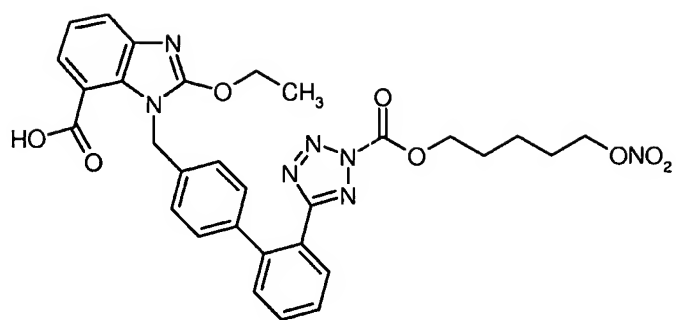
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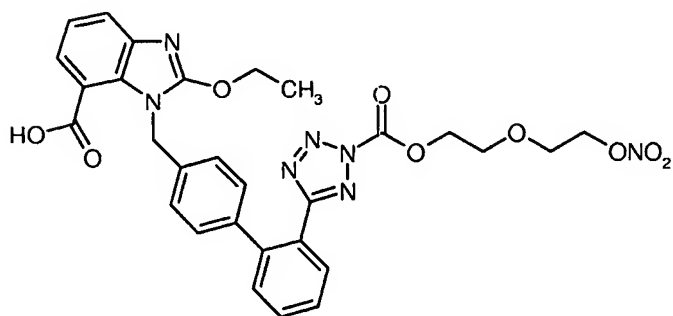
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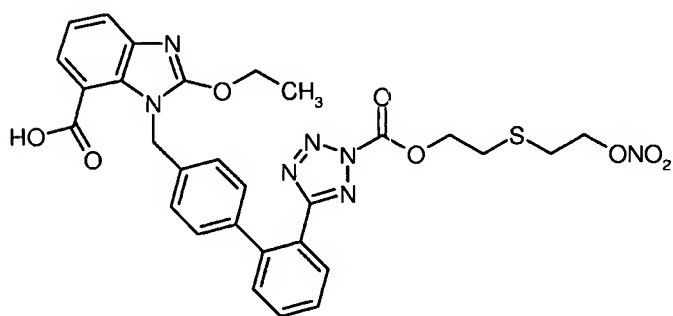
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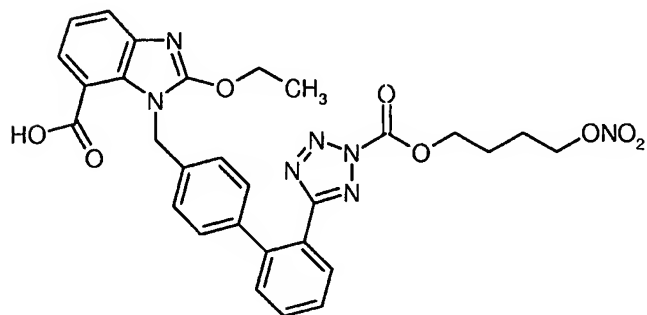
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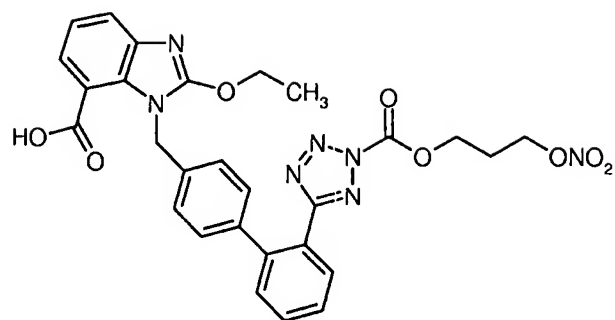
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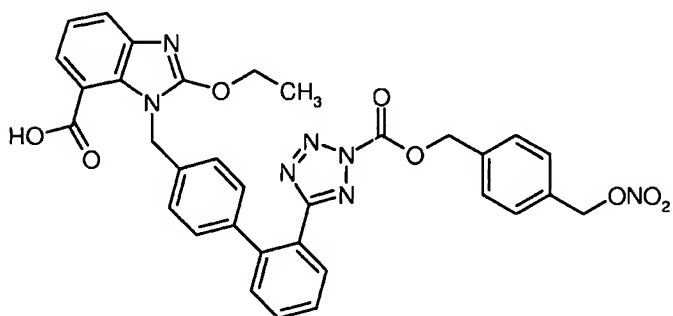
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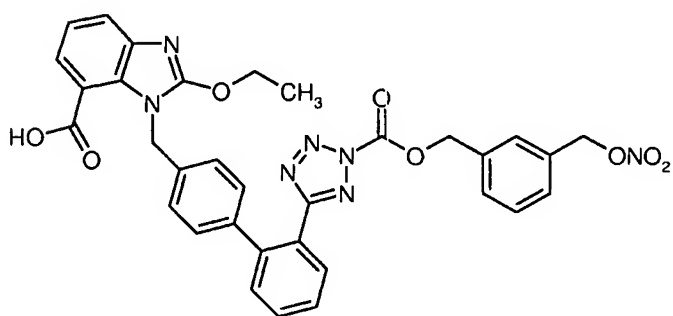
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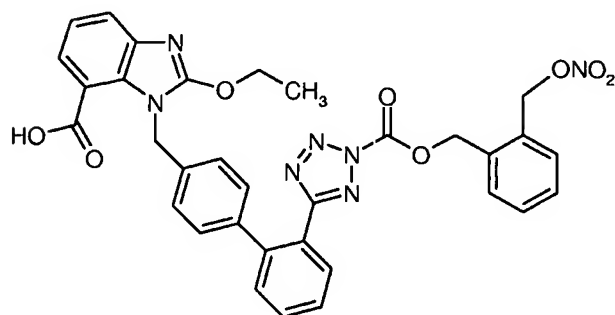
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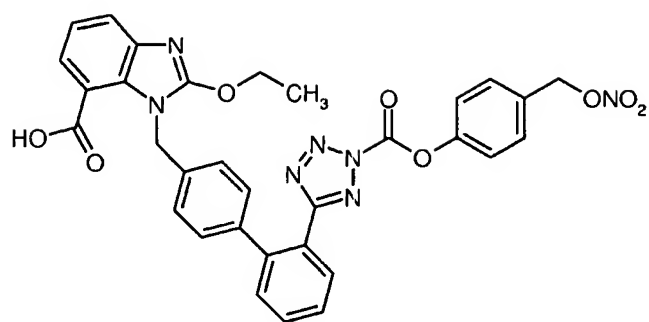
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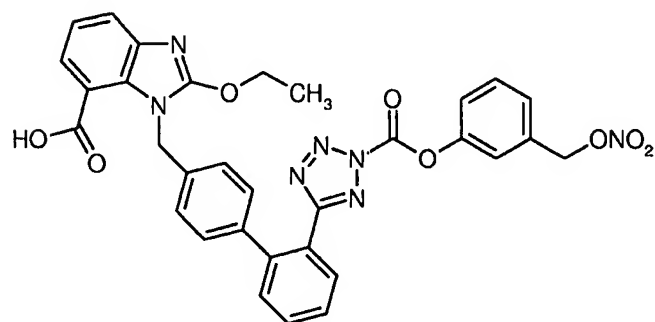
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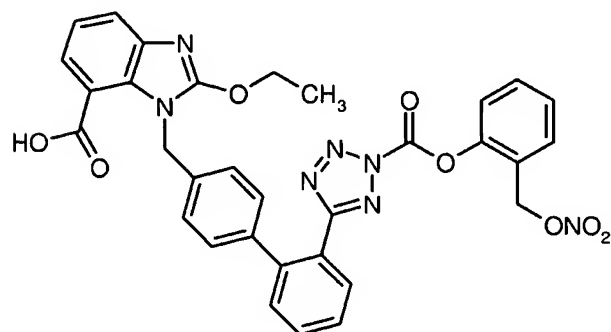
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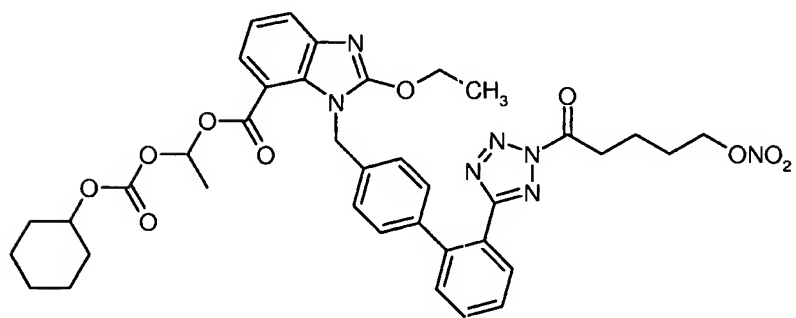
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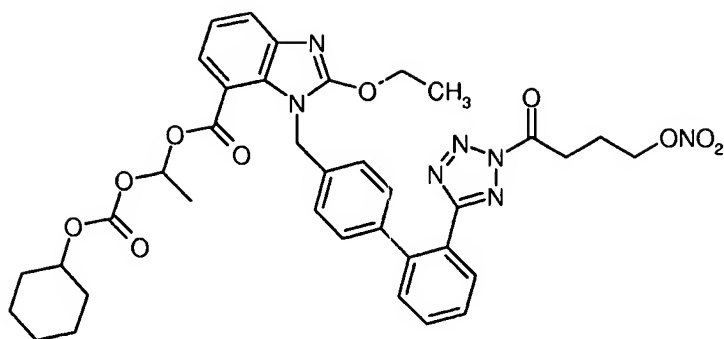
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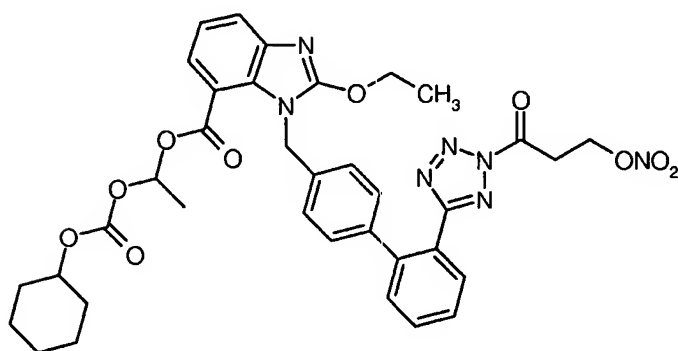
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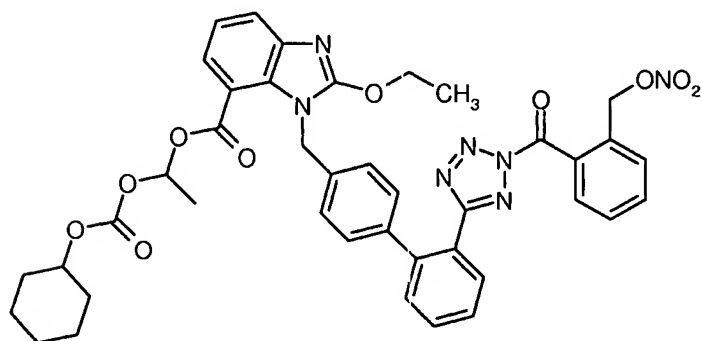
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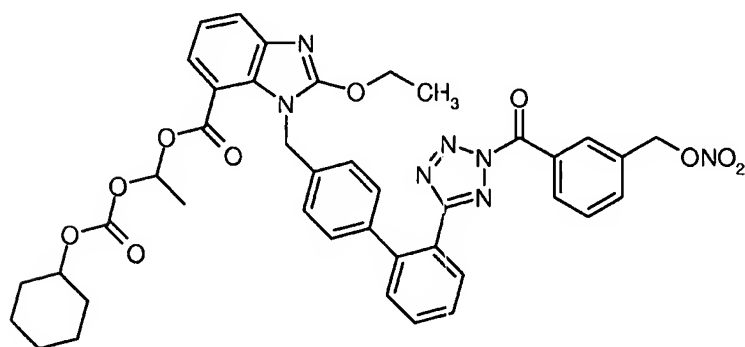
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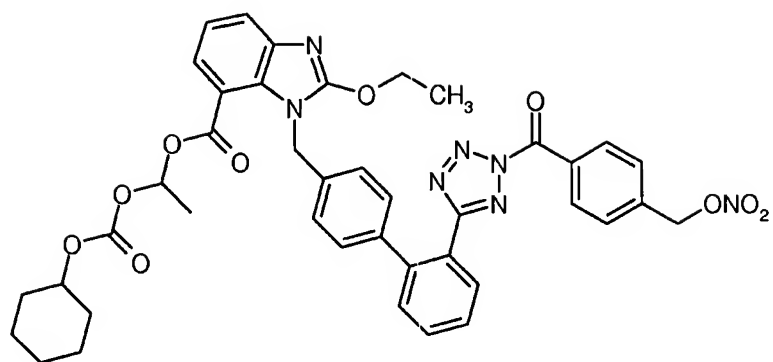
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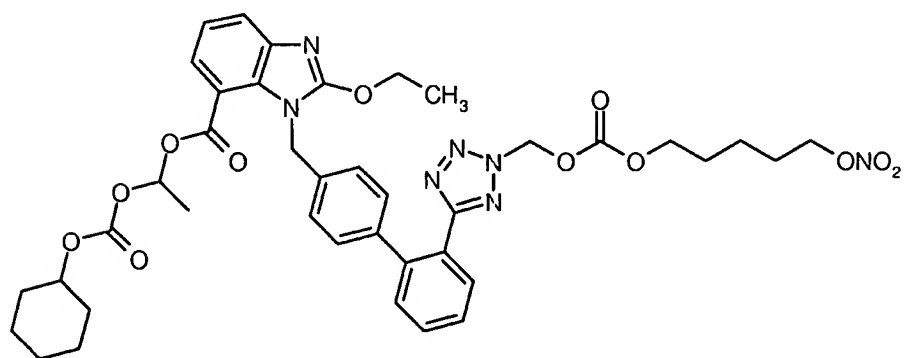
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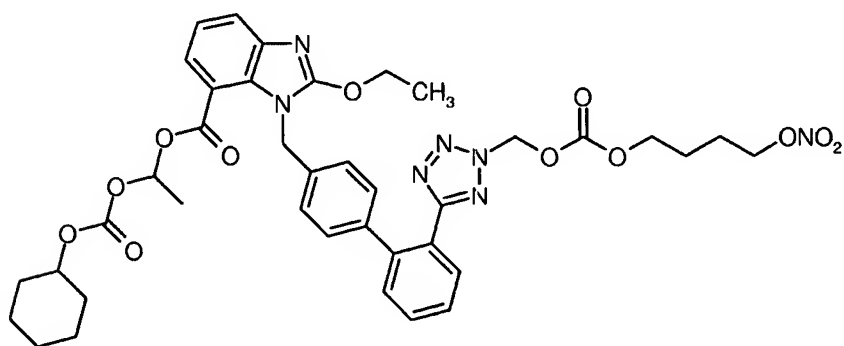
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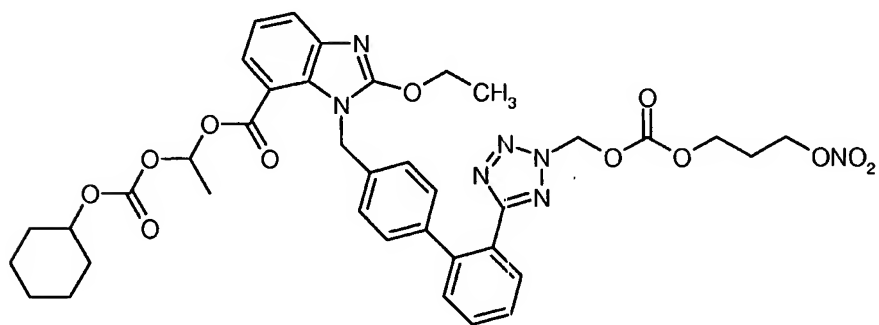
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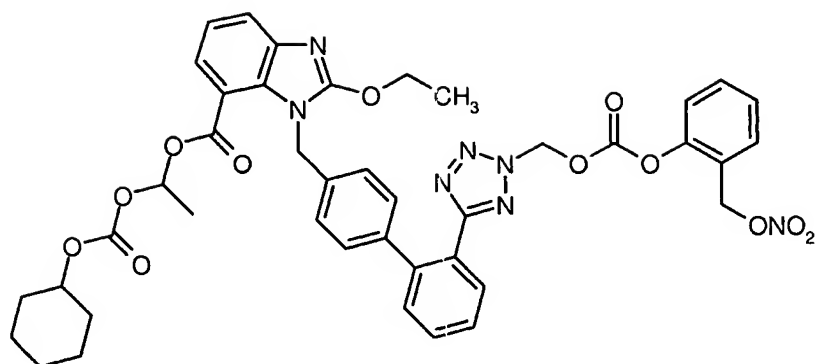
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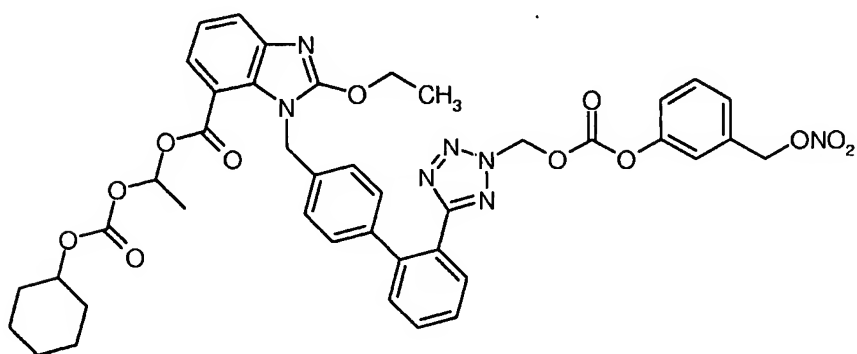
(101)



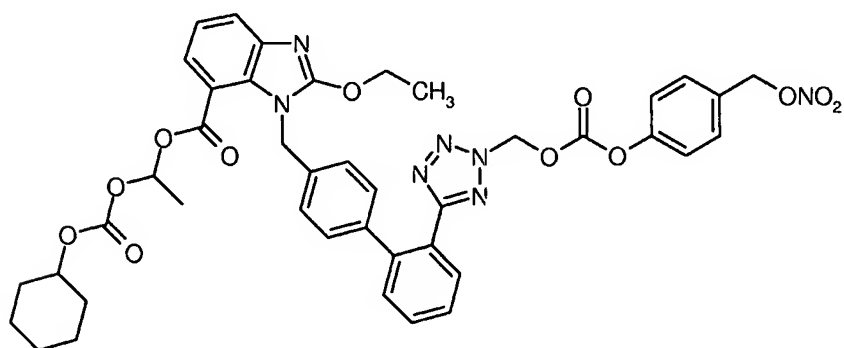
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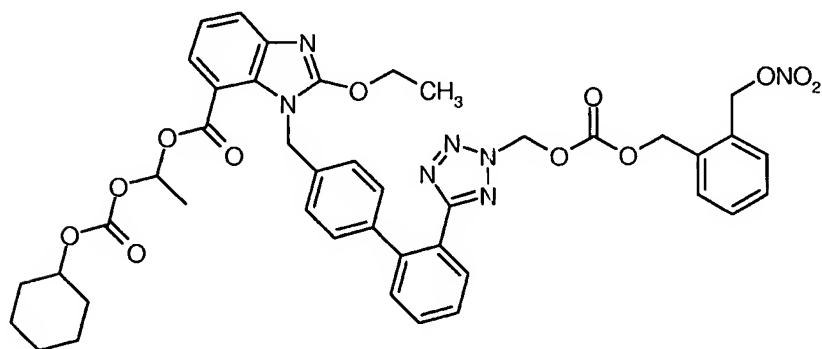
(103)



(104)

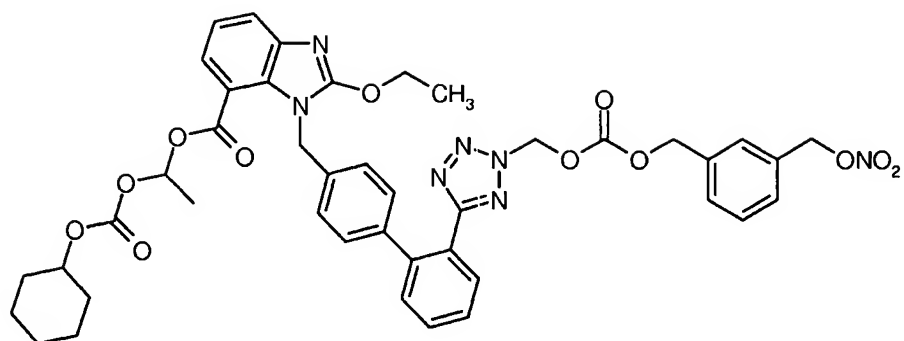


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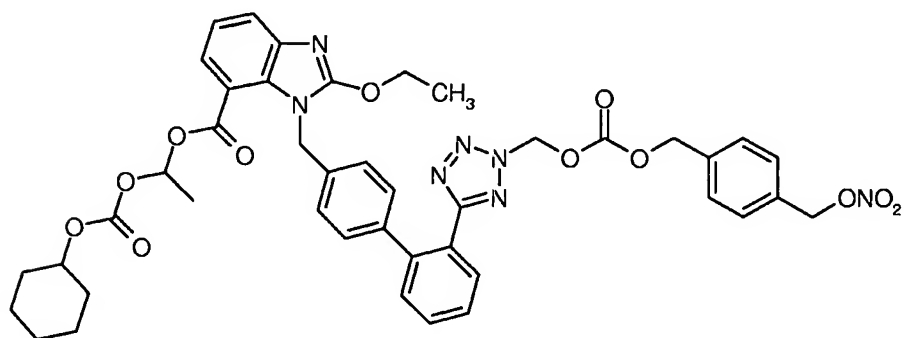


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(106)

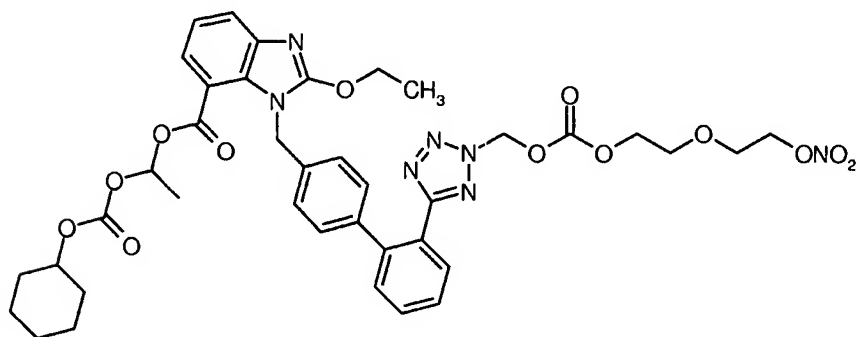


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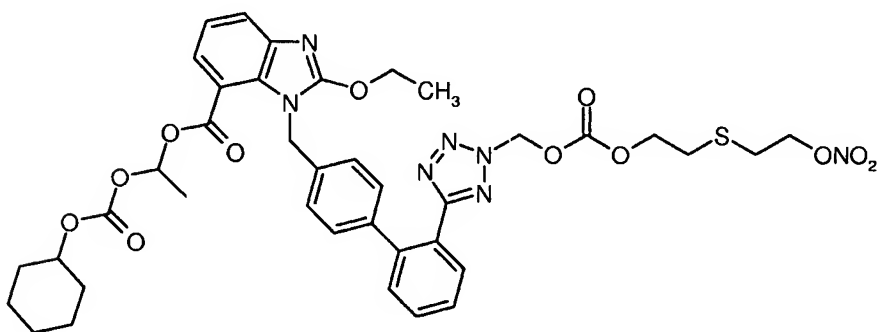


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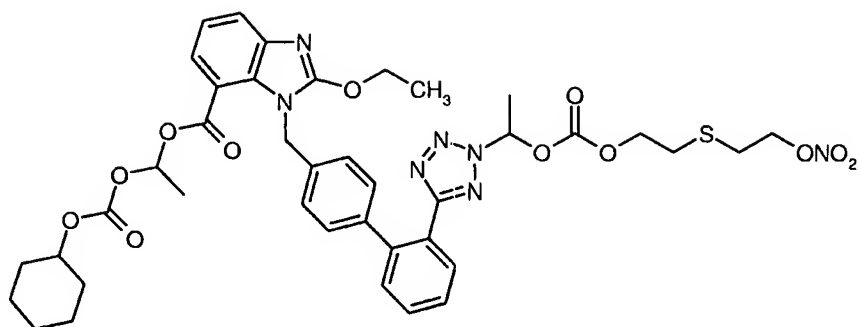
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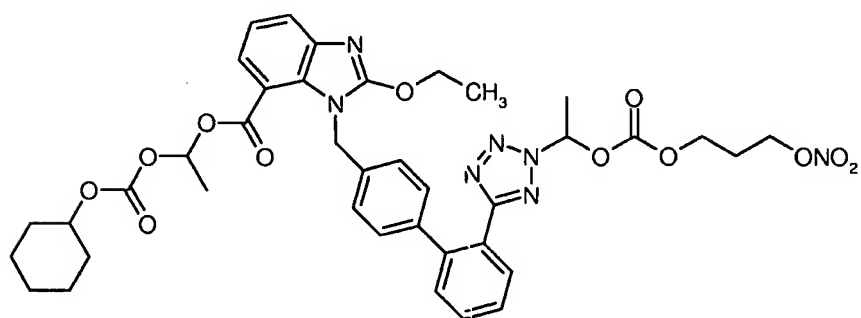
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(110)

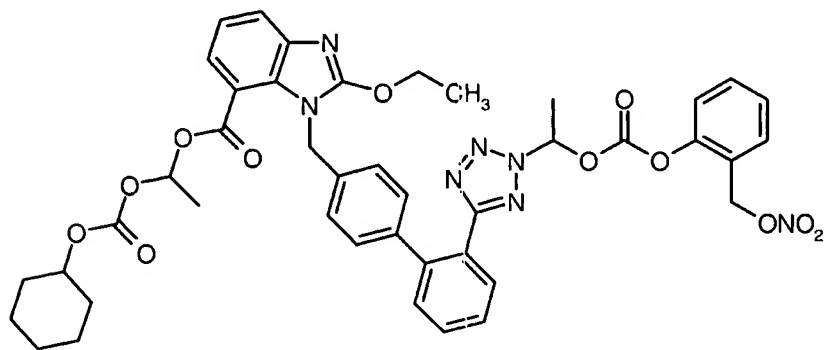


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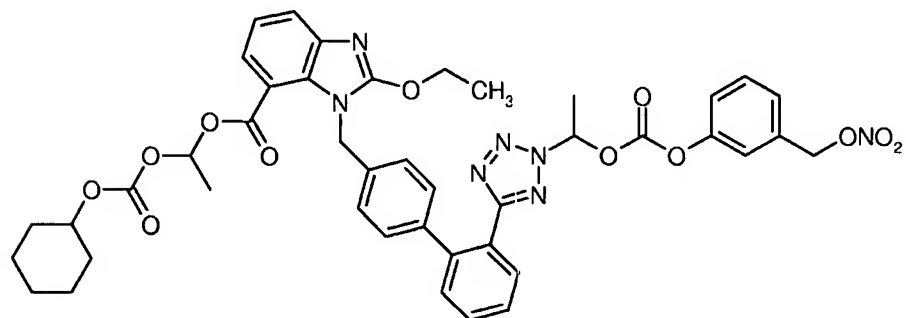


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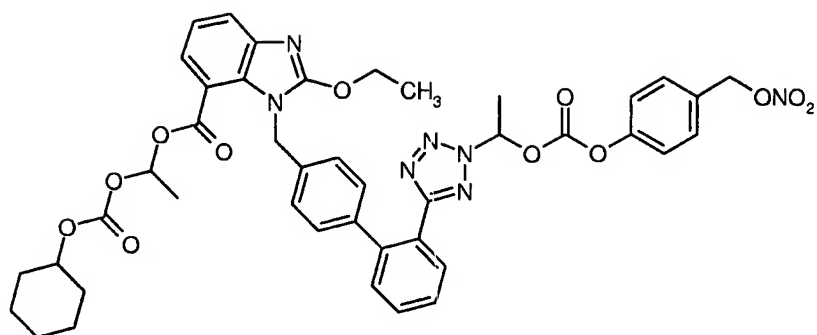
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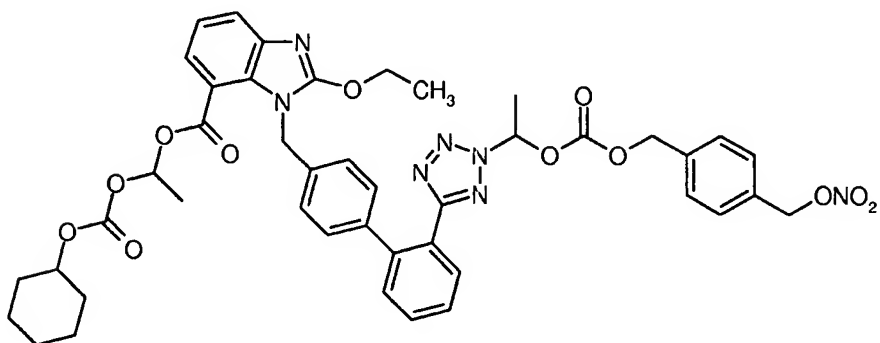
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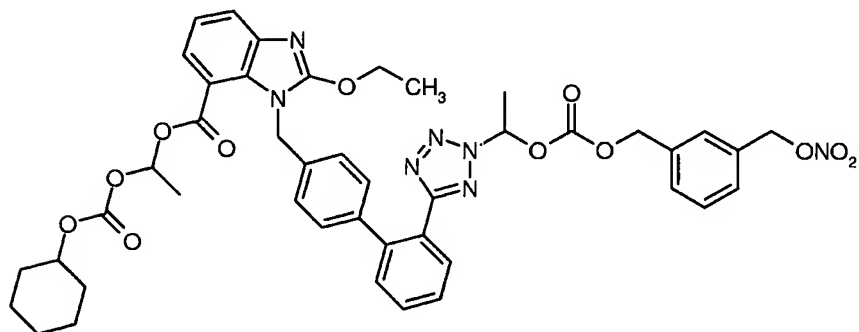
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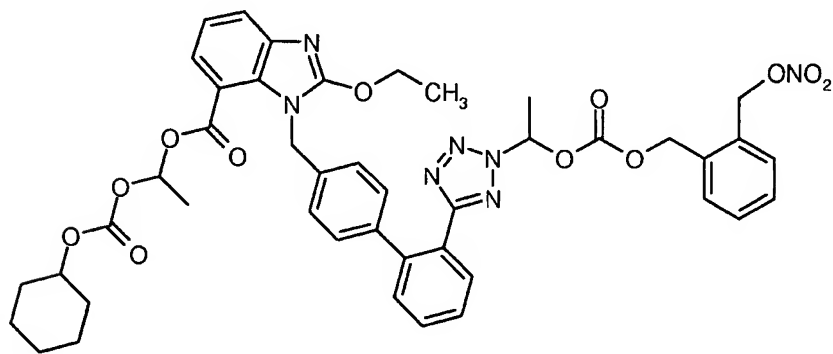
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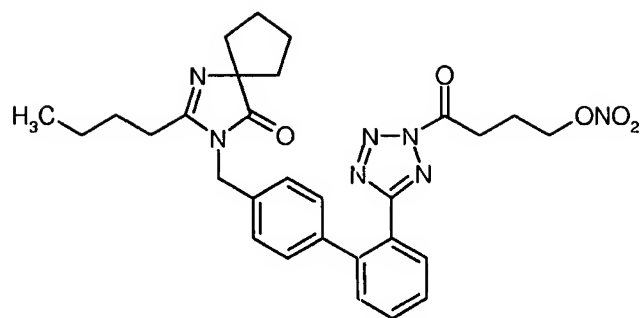
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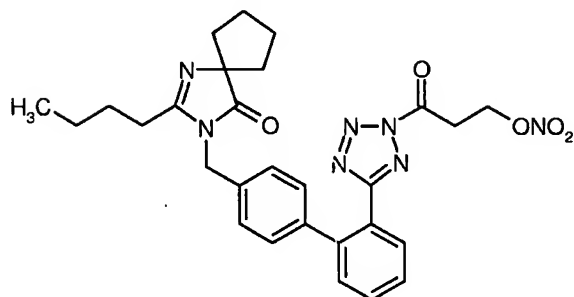
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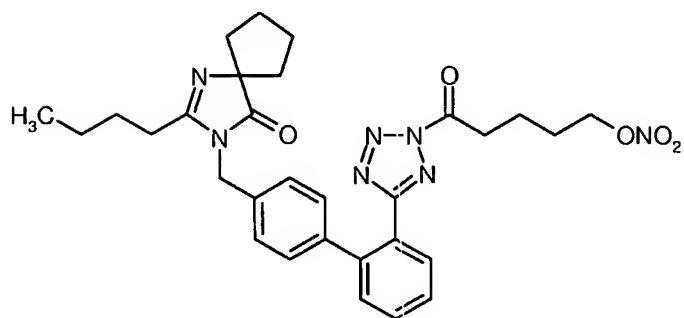
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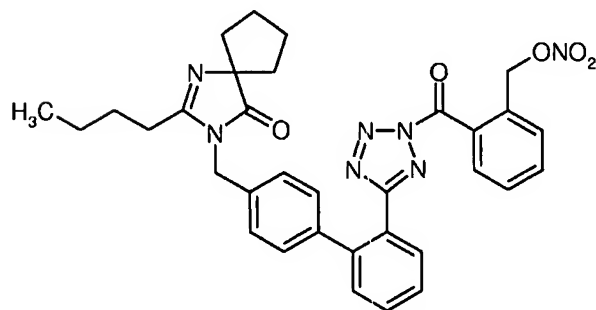
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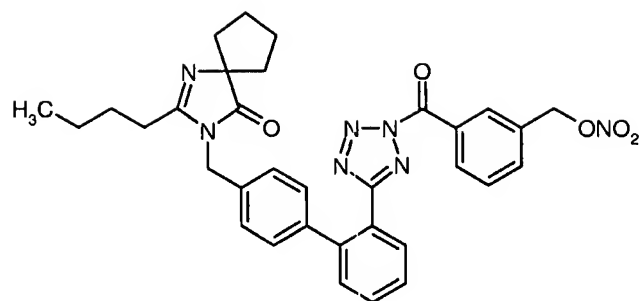
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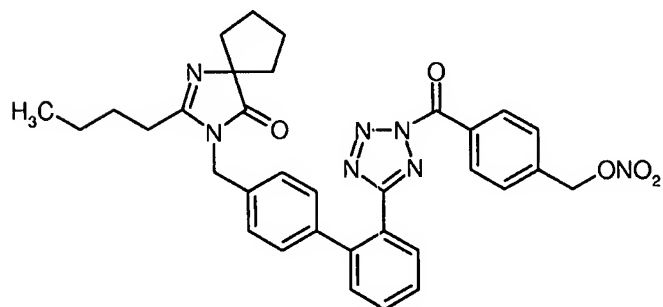
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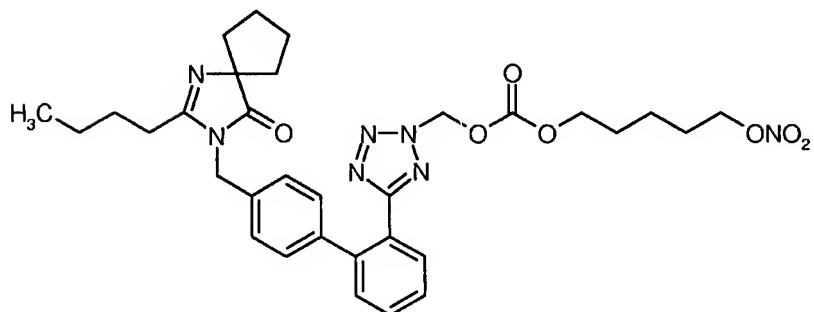
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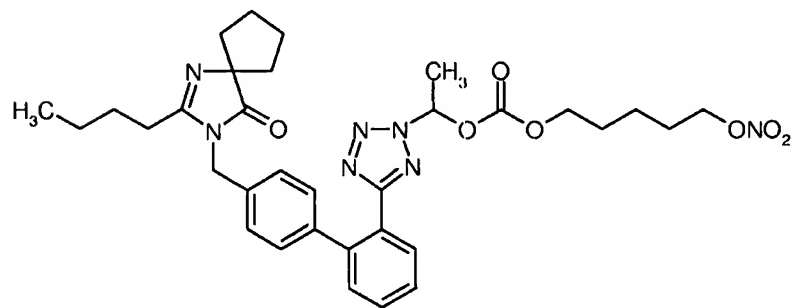
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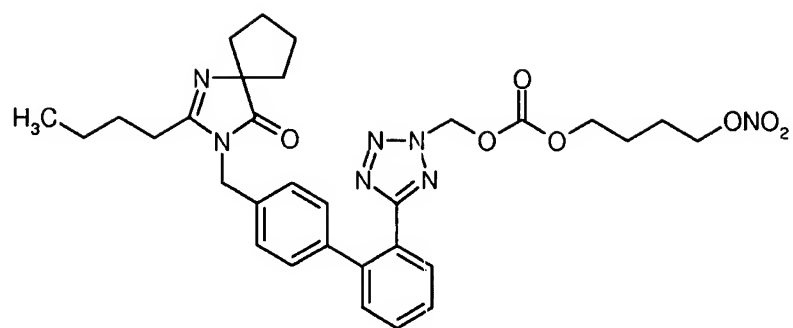
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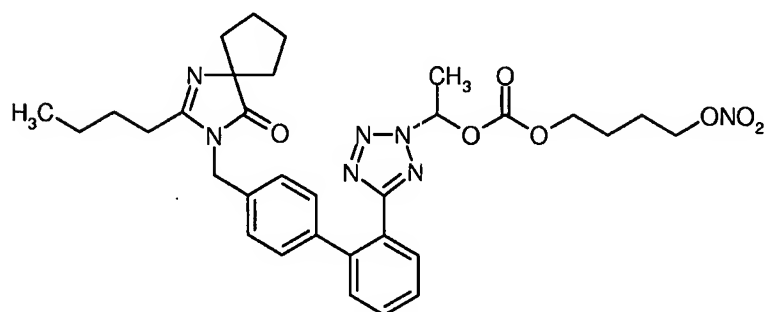
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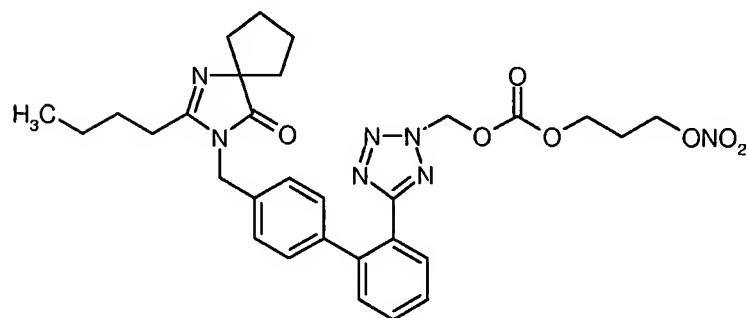
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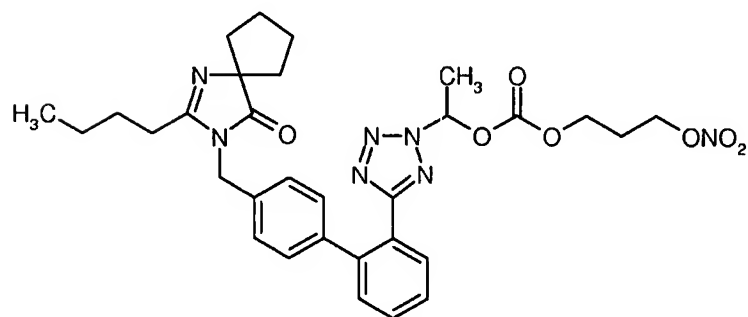
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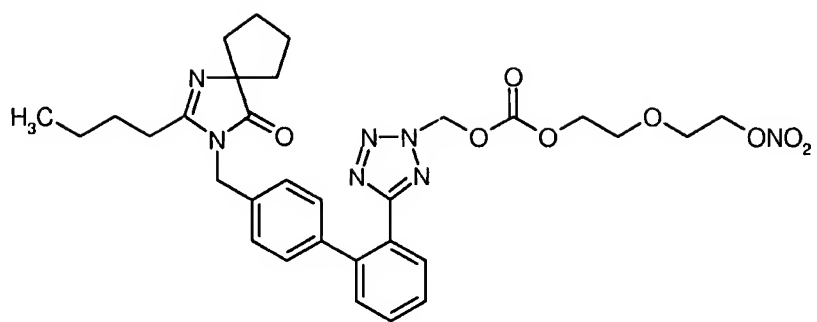
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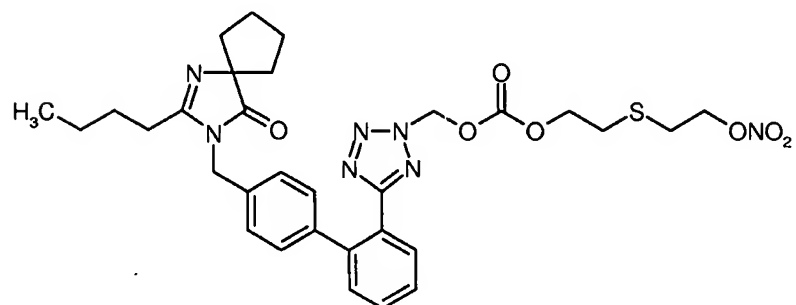
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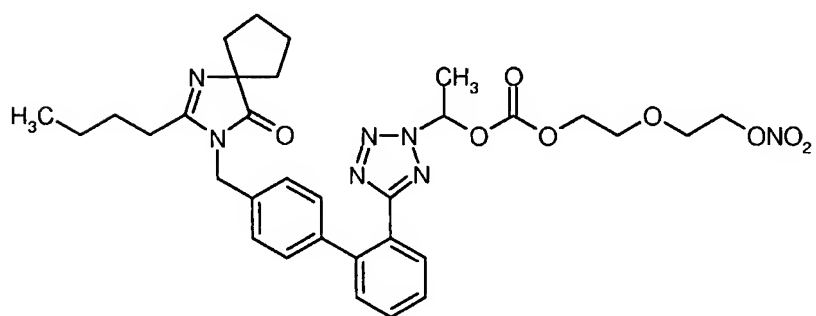
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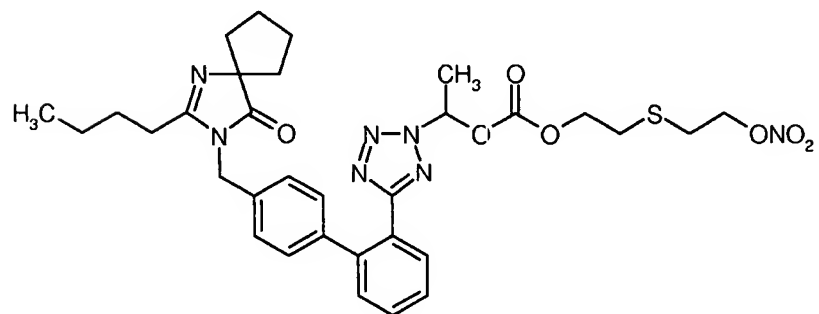
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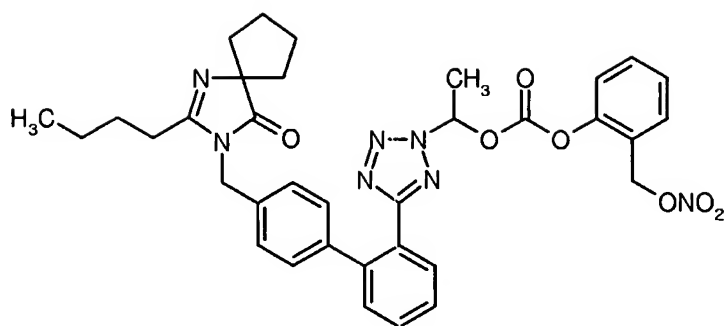
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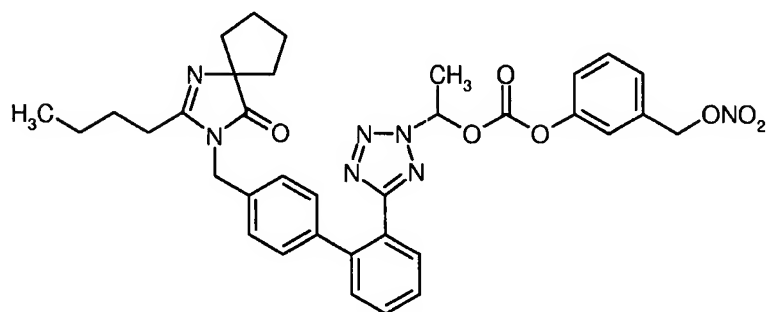
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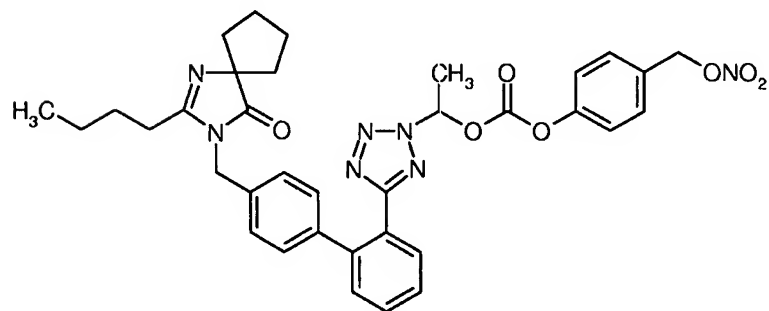
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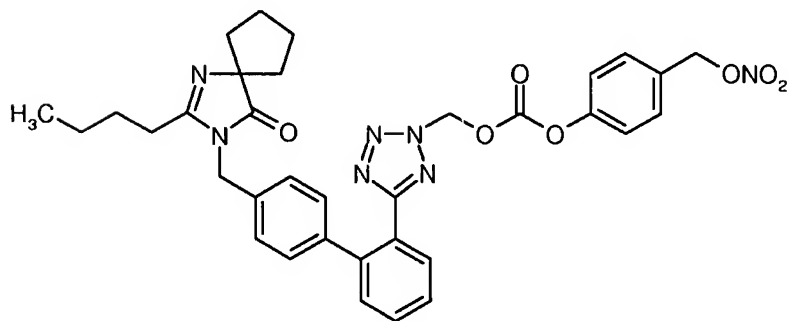
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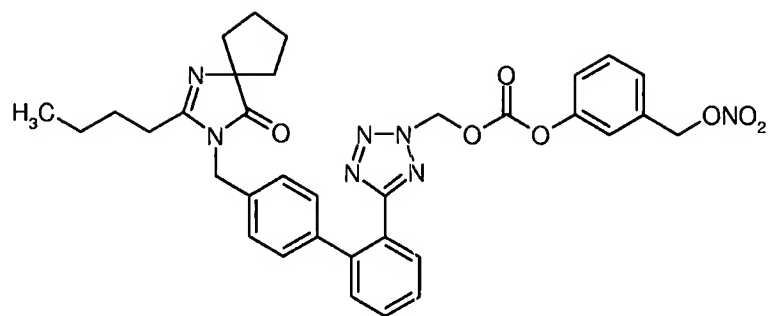
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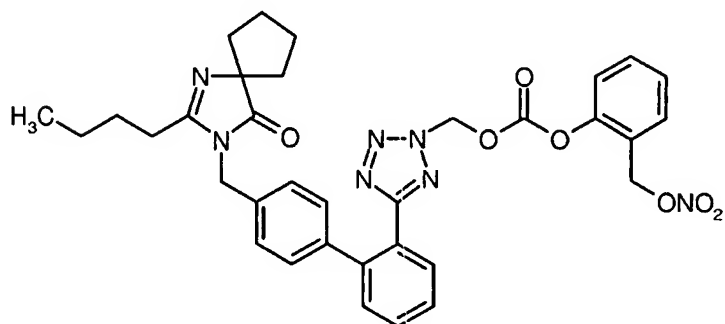
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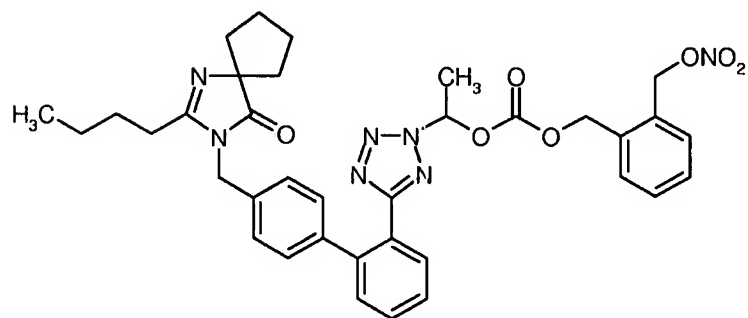
(138)



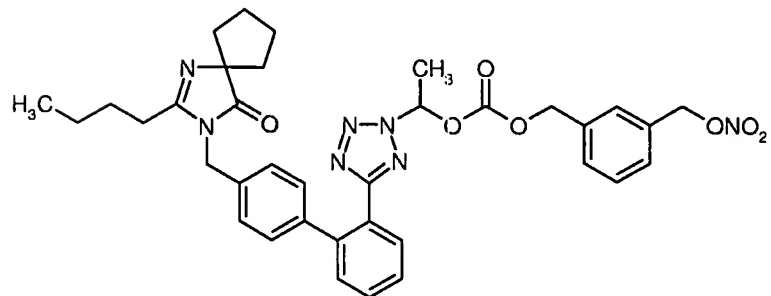
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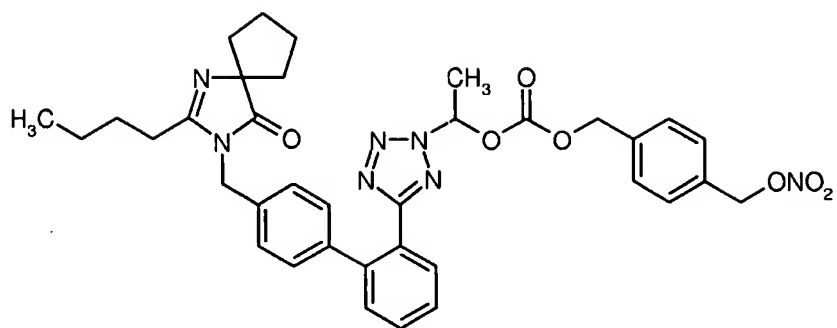
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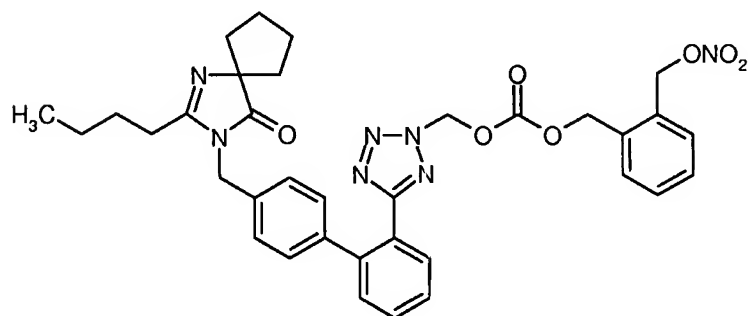
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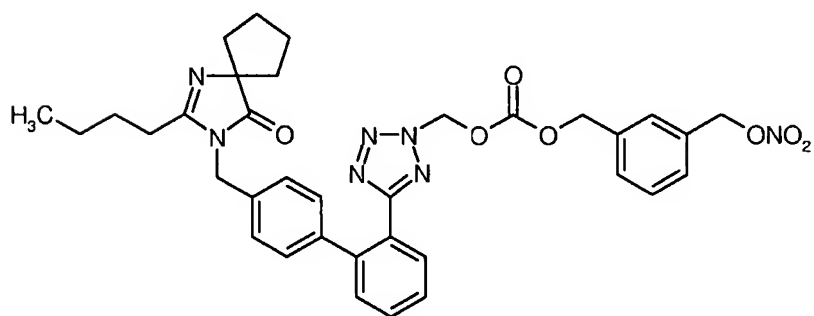
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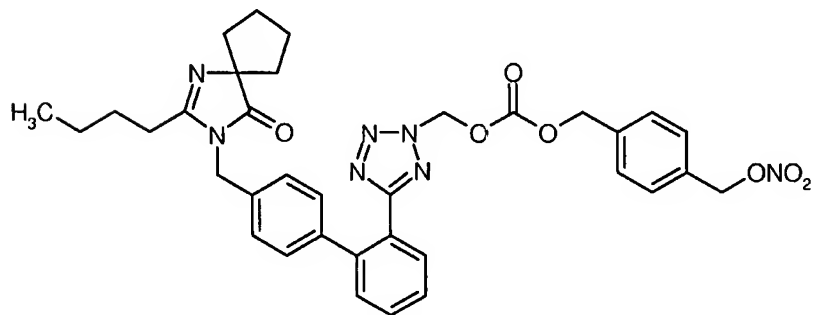
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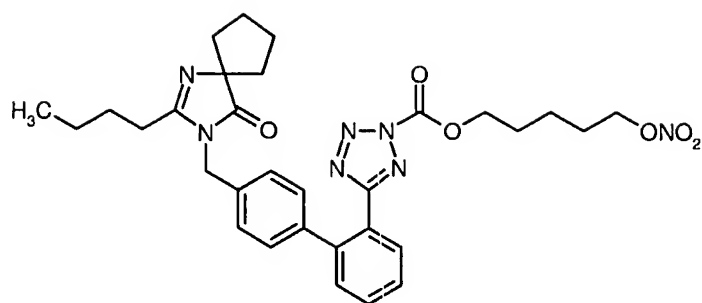
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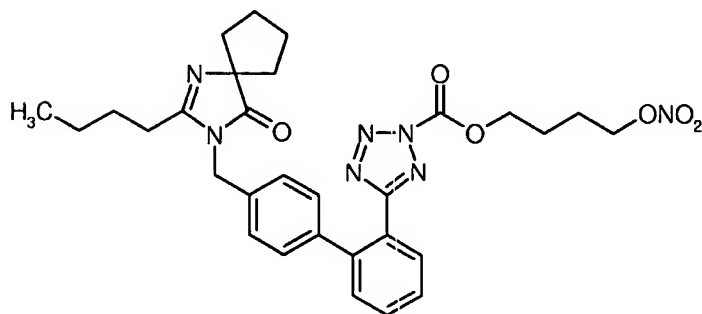
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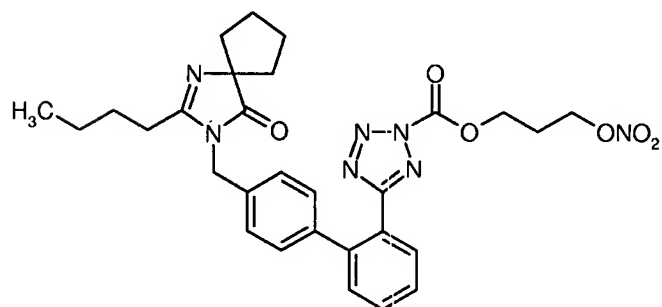
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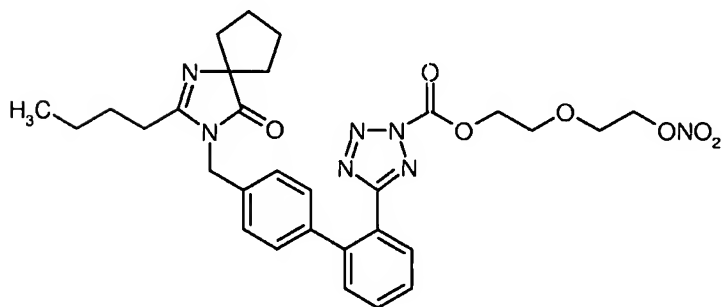
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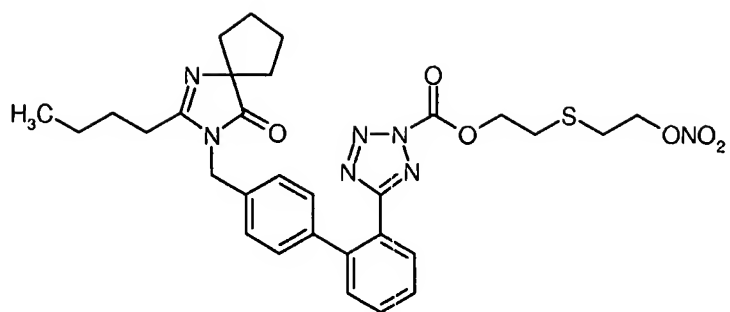
(148)



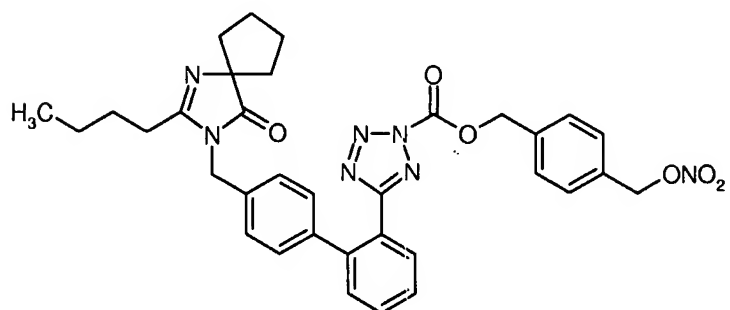
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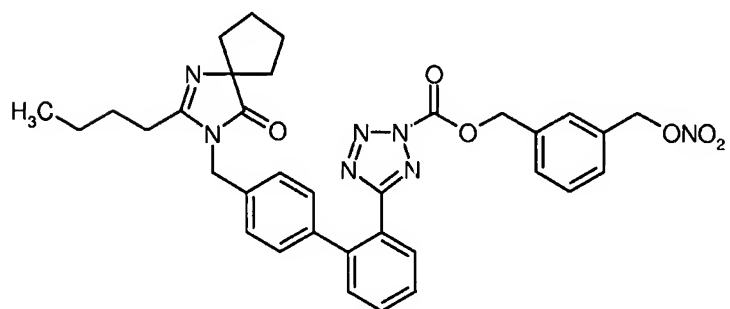
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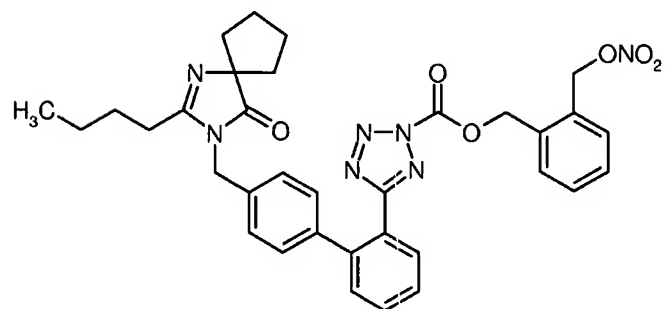
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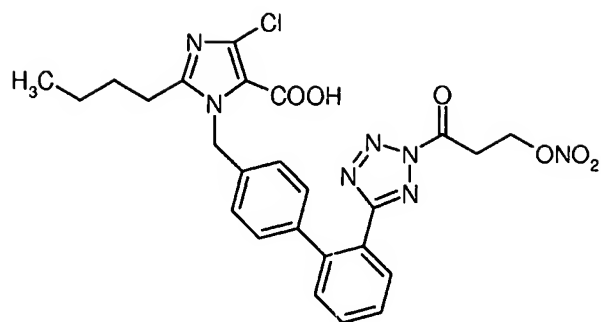
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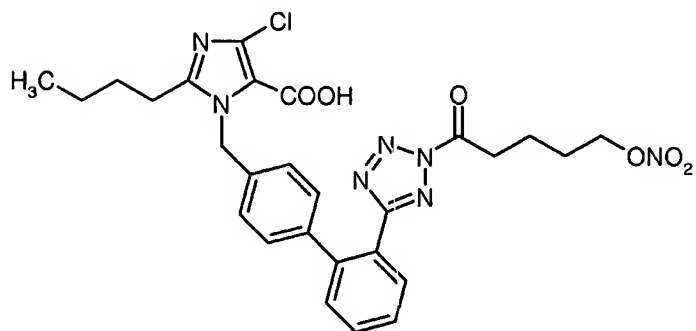
(153)



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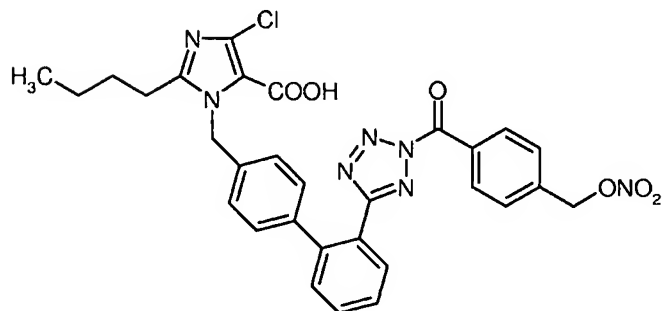


(159)

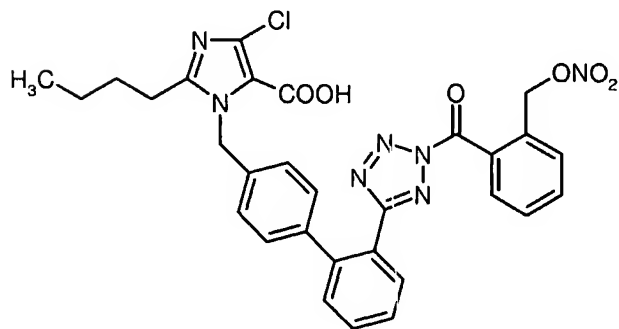


(160)

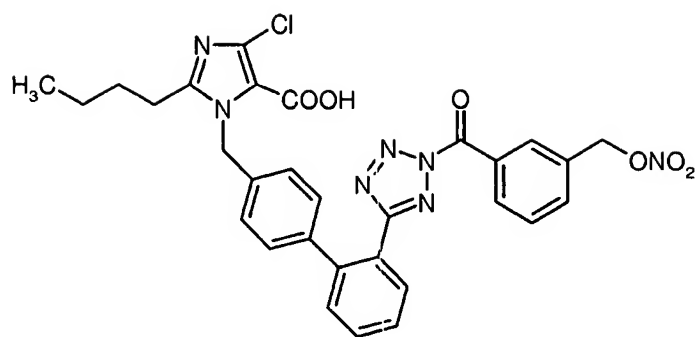
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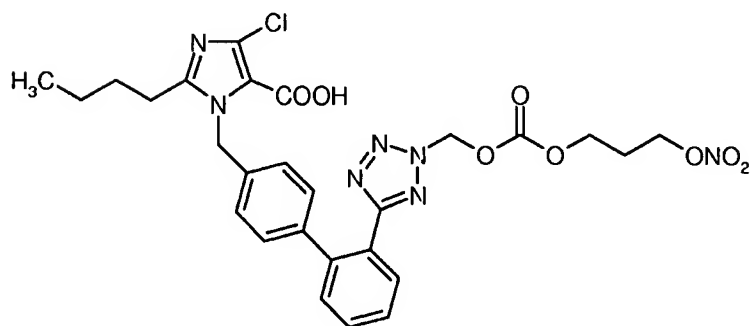
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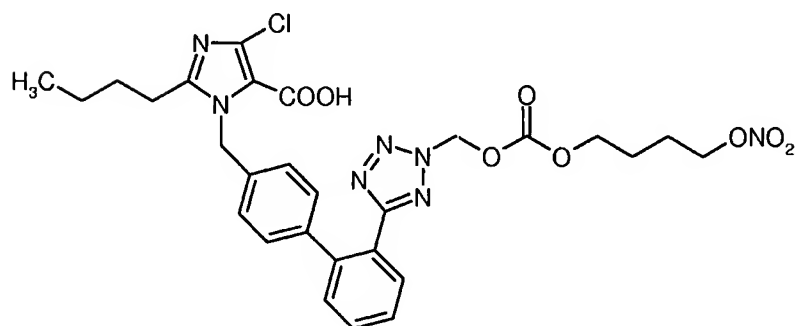
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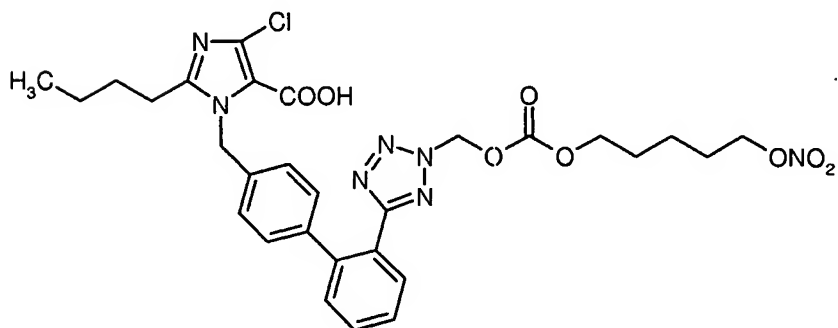
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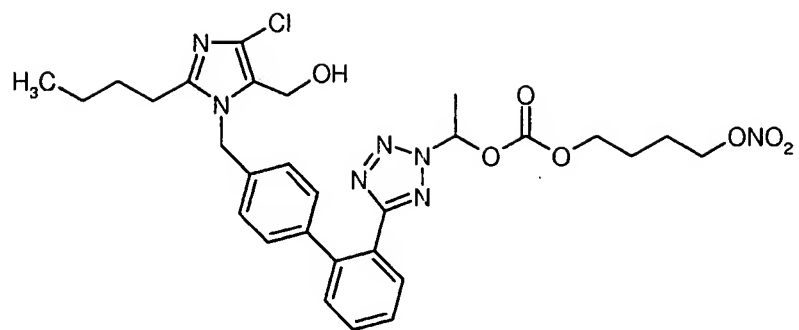
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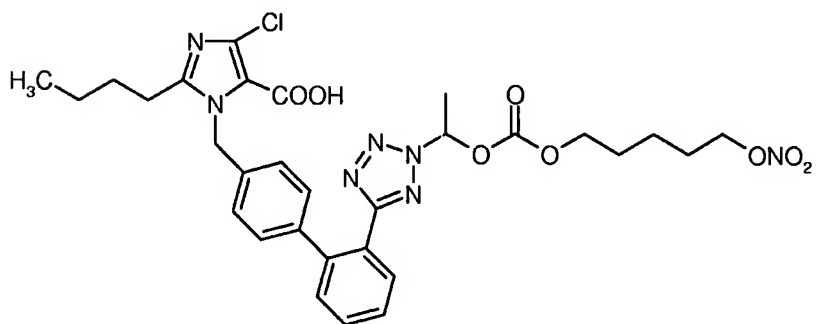
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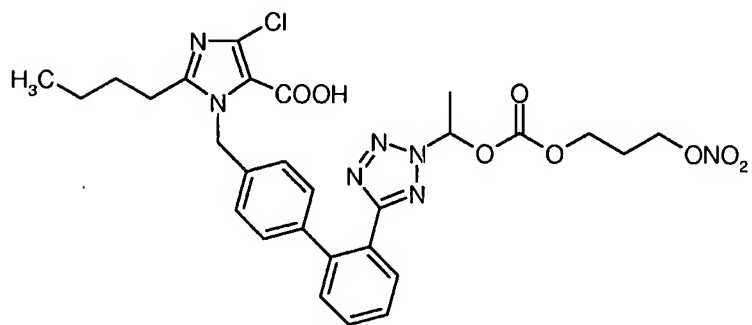
(166)



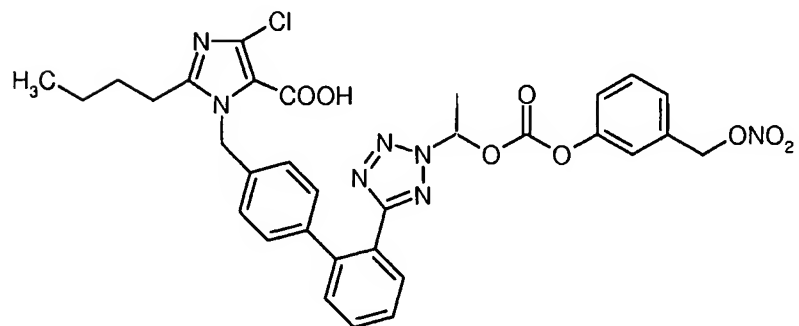
(167)



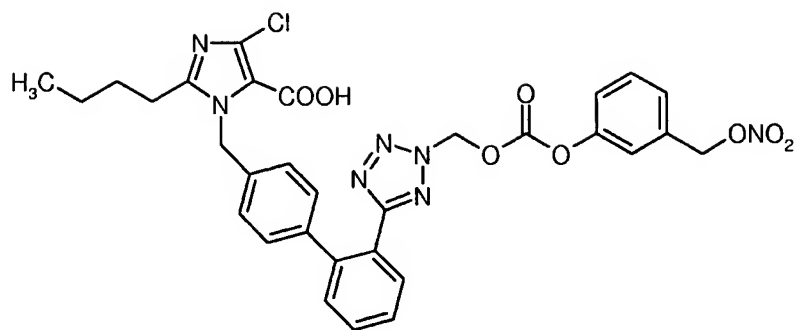
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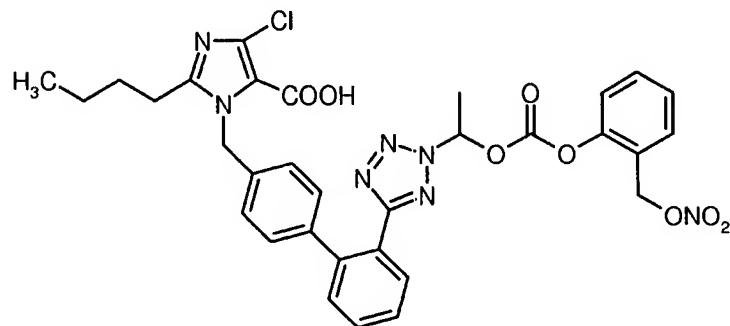
(169)



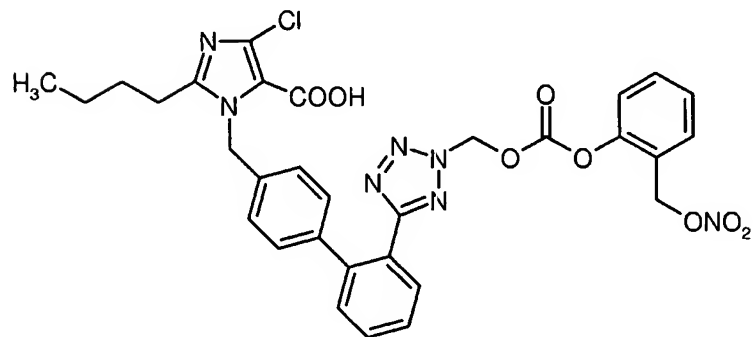
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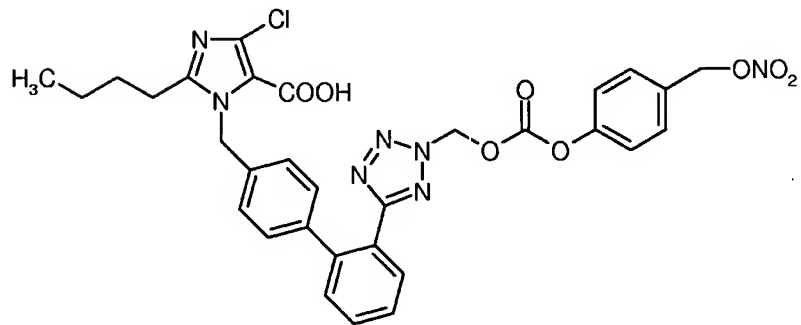
(171)



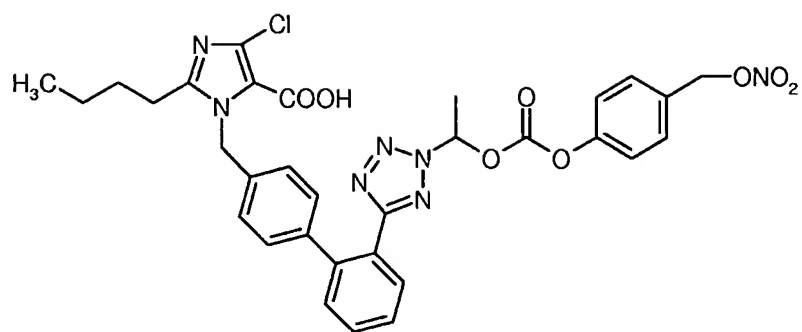
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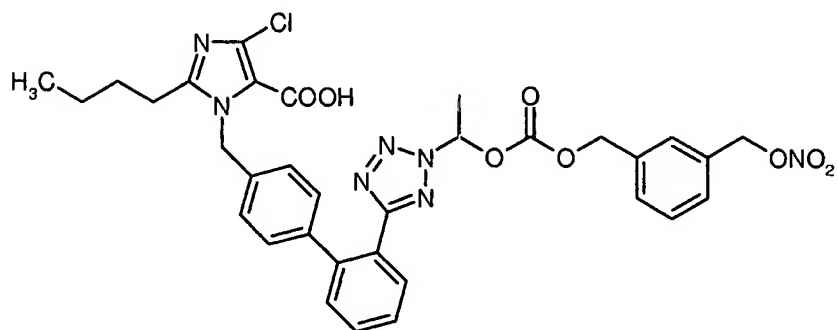
(173)



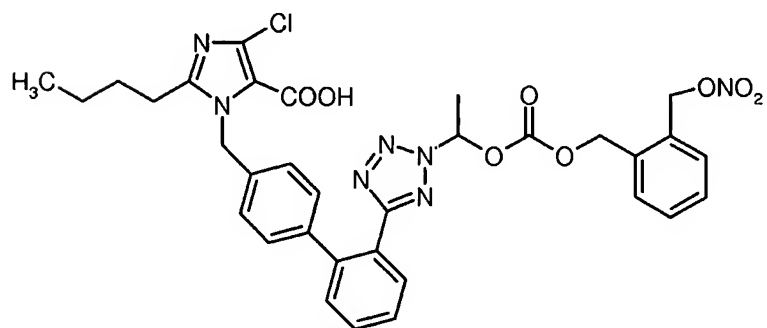
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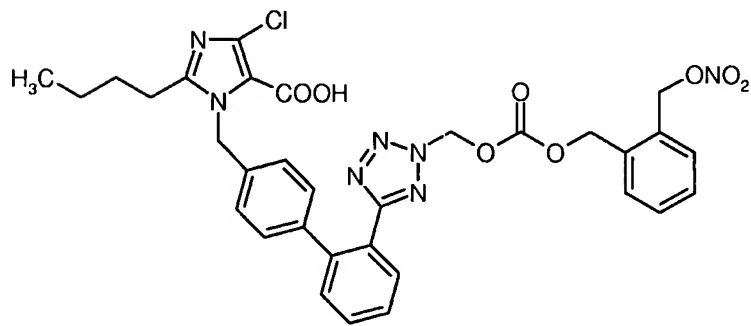
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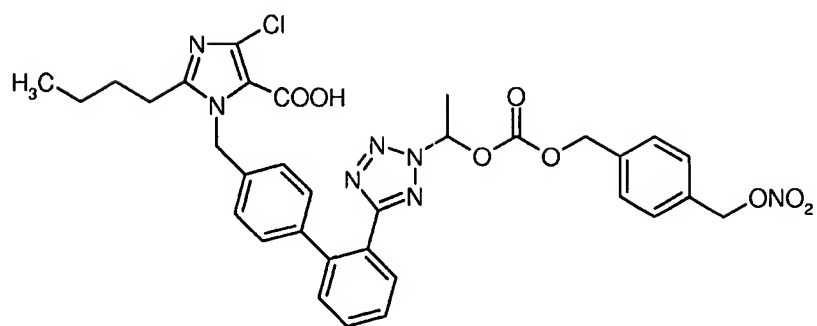
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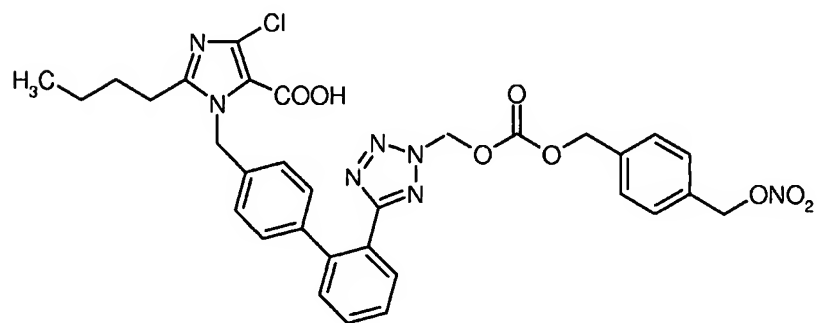
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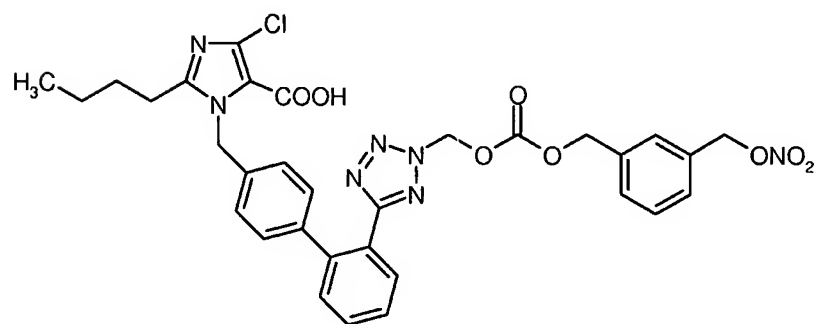
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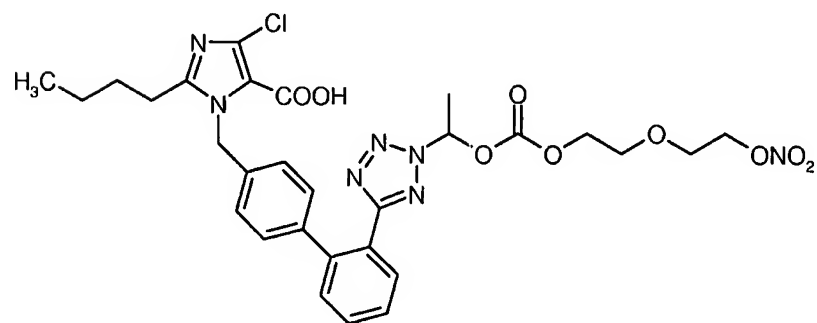
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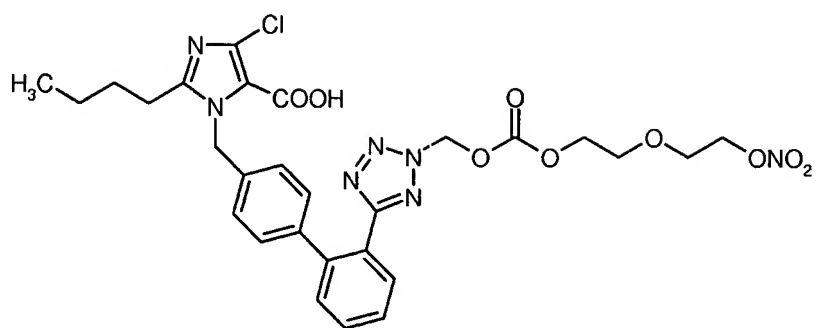
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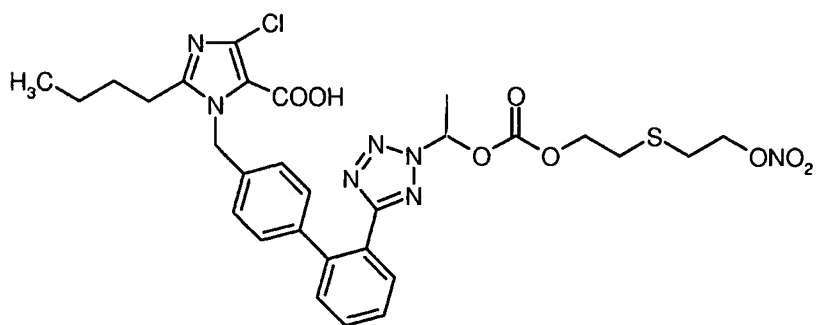
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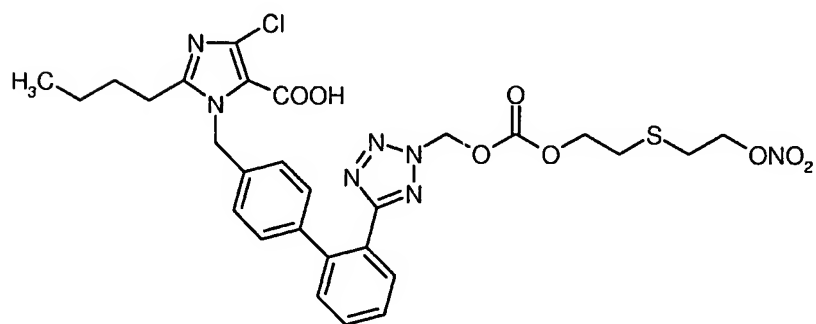
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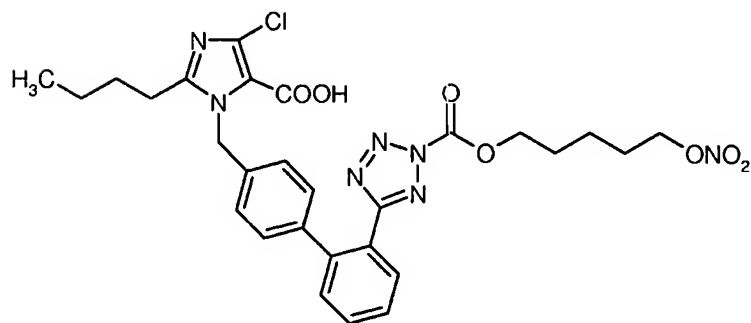
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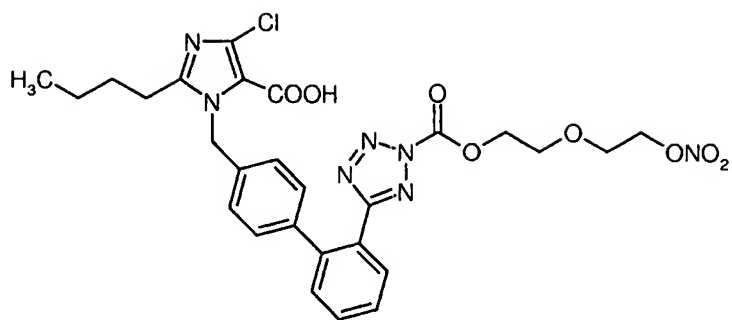
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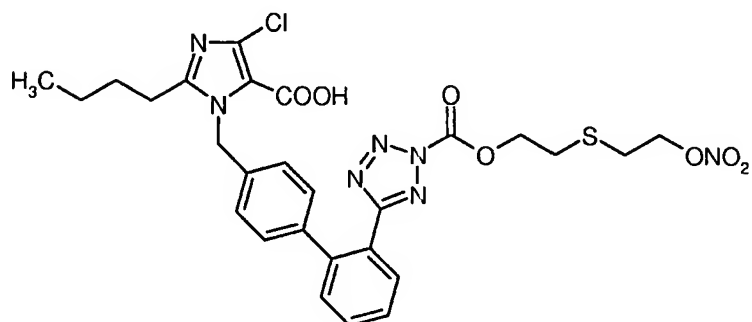
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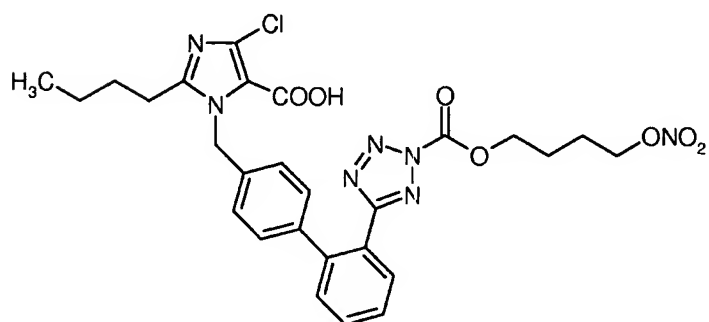
(186)



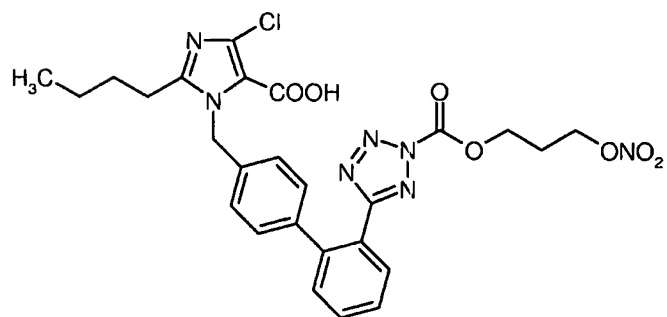
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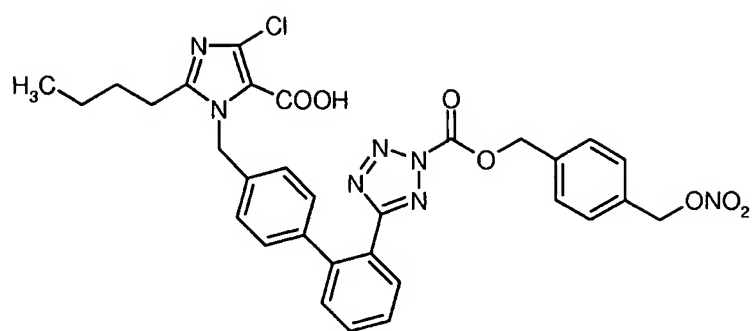
(188)



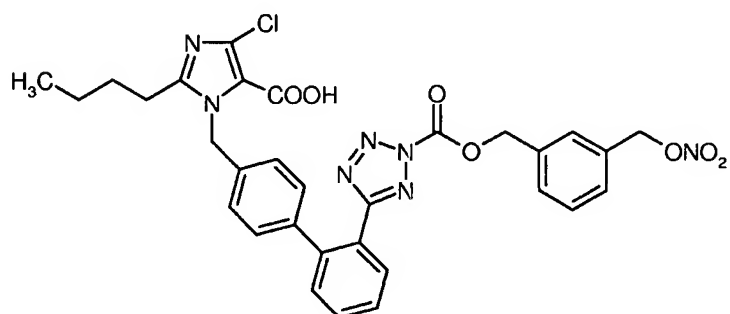
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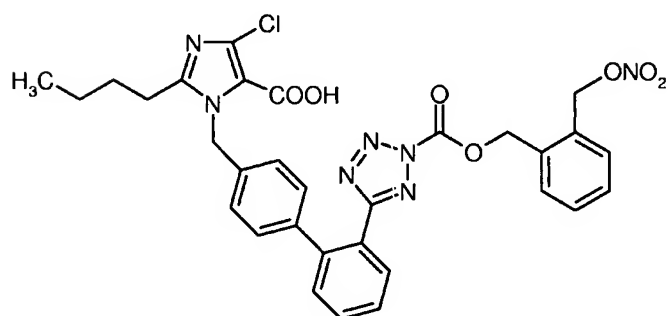
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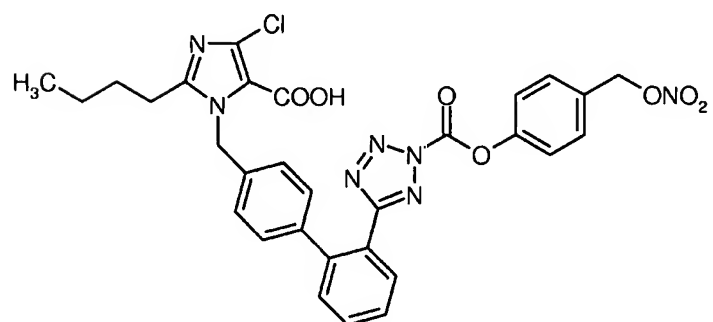
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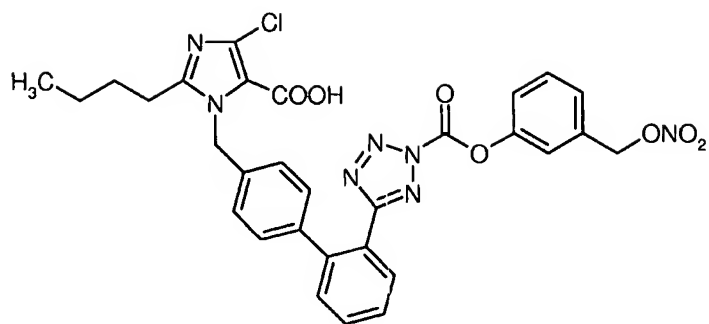
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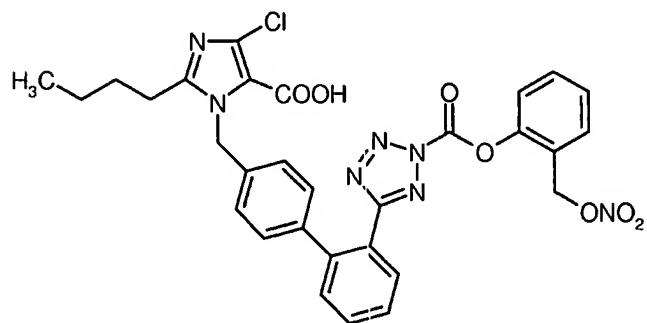
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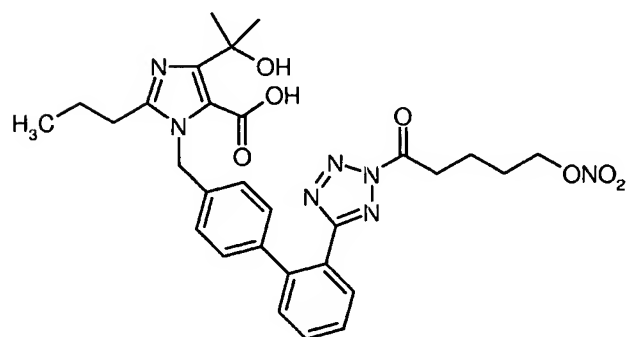
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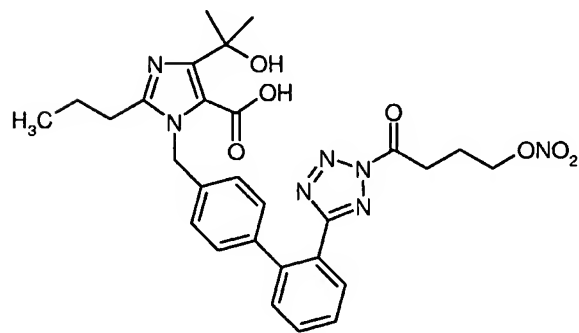
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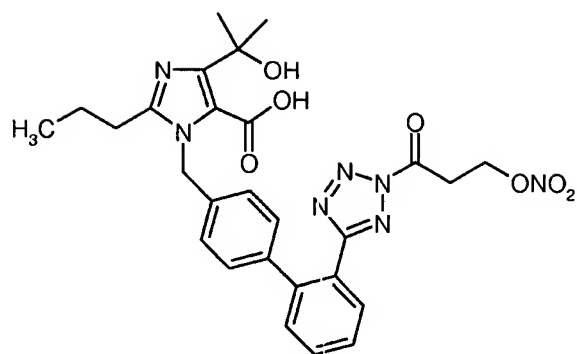
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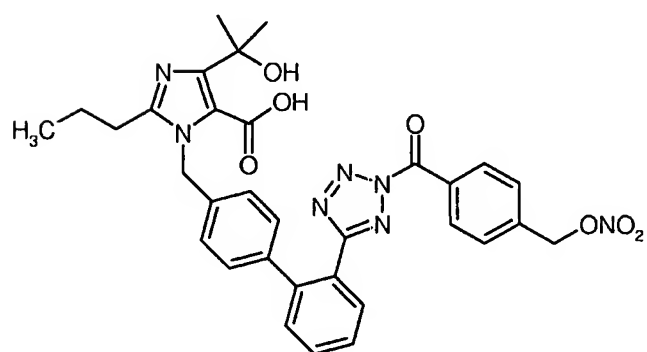
(197)



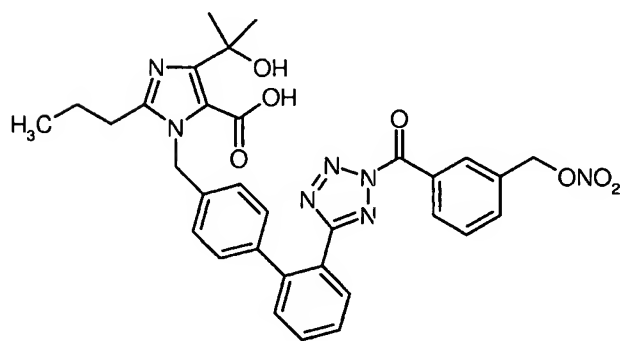
(198)



(199)

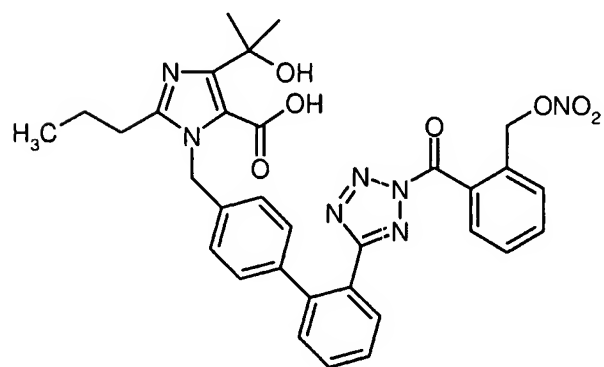


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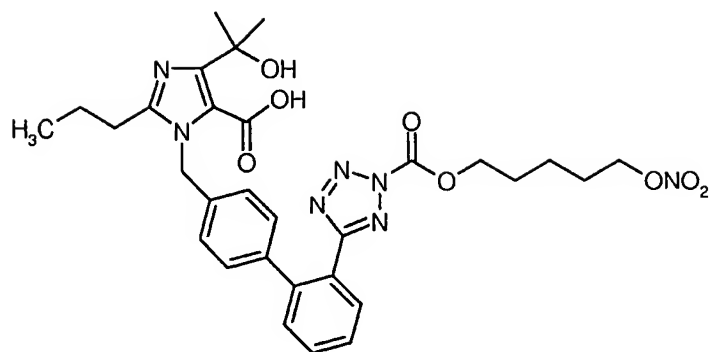
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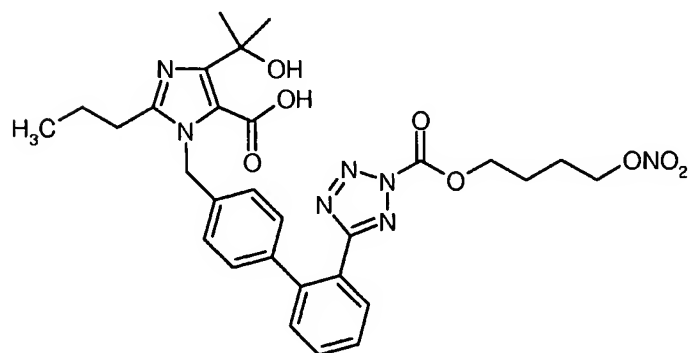


254

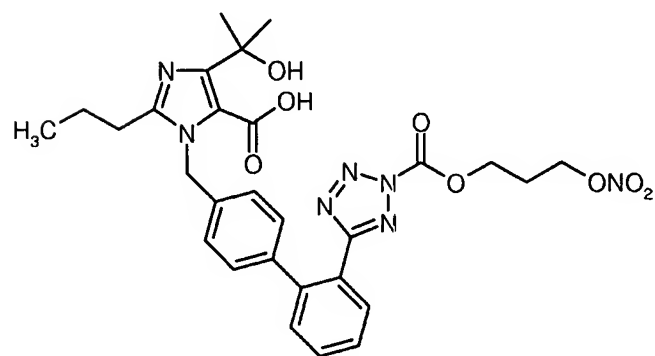
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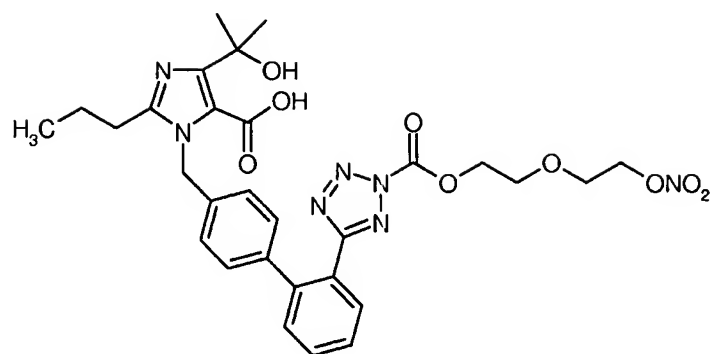
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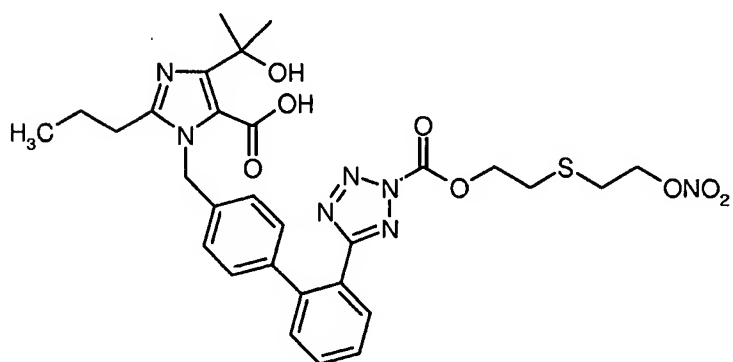
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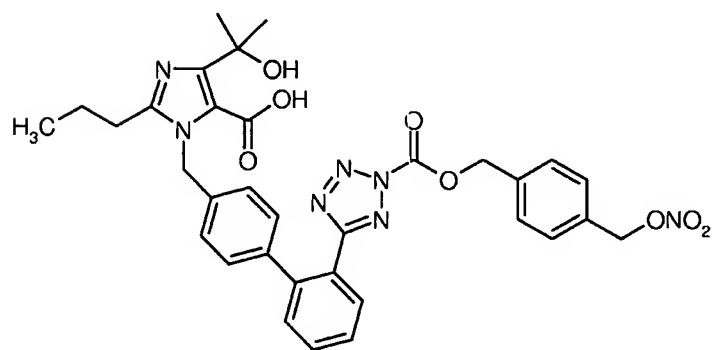
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(206)

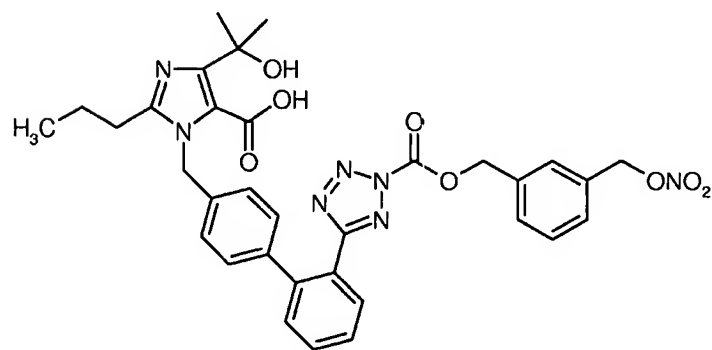


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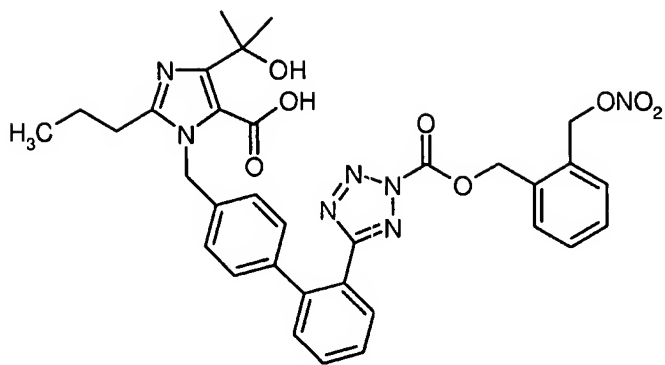


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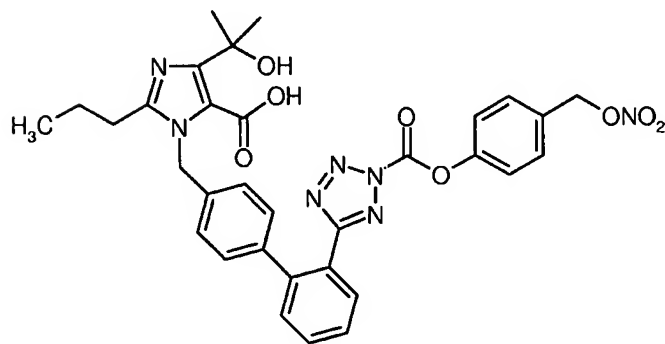
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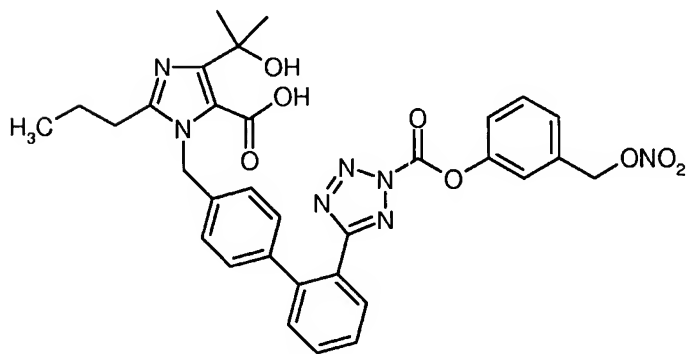
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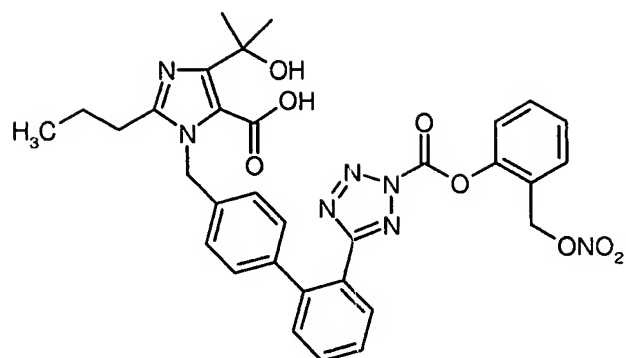
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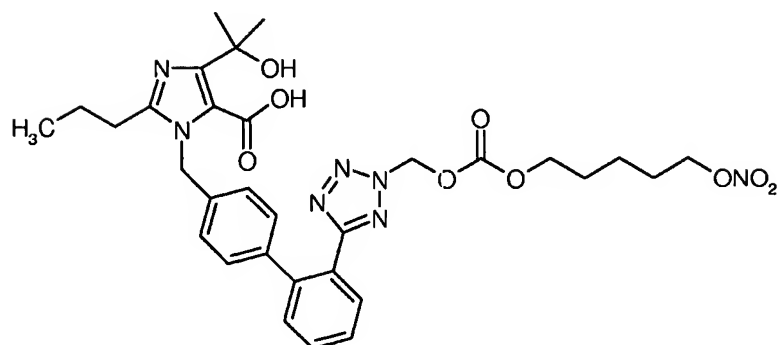
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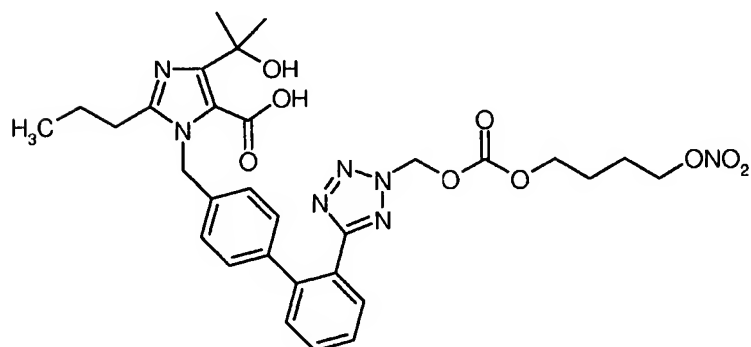
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(213)

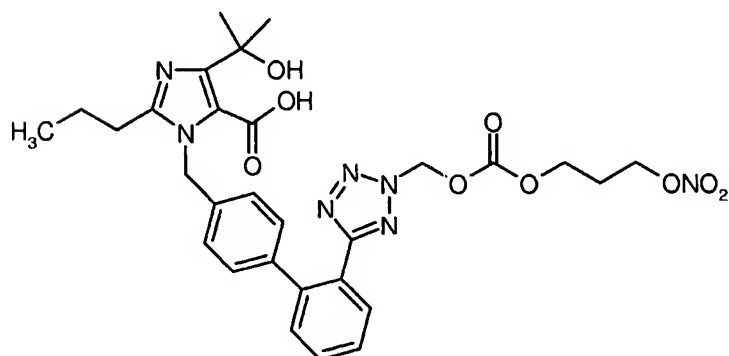


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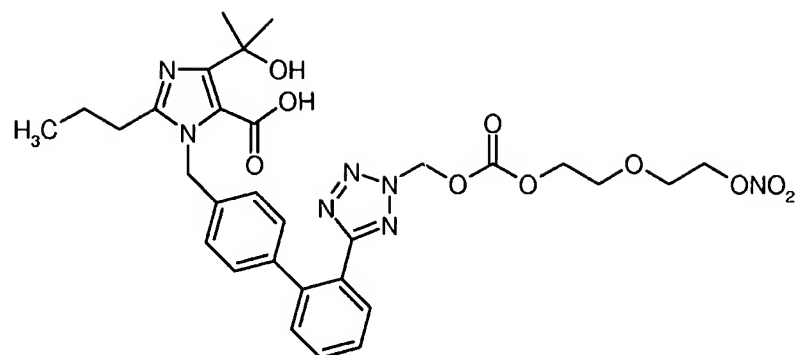
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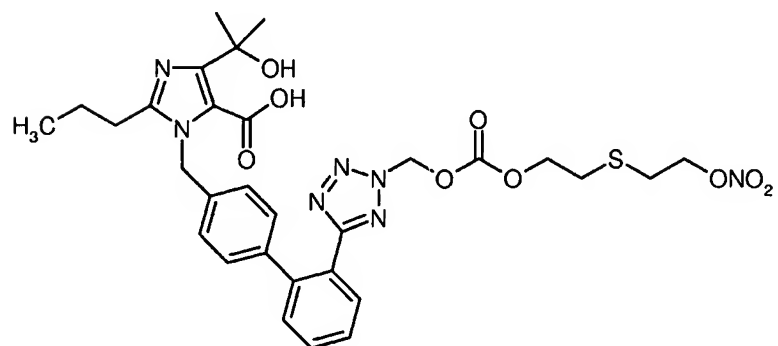


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(215)

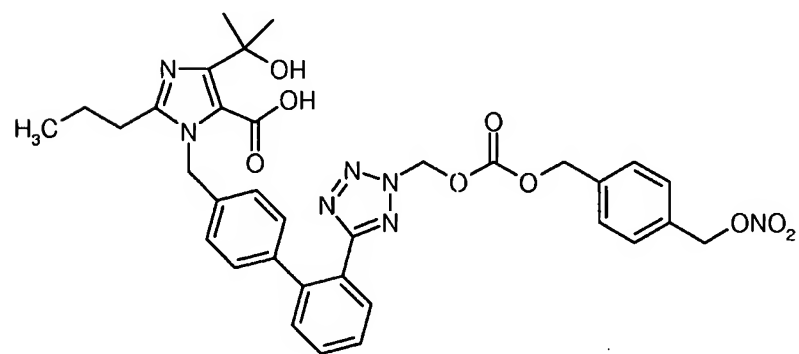


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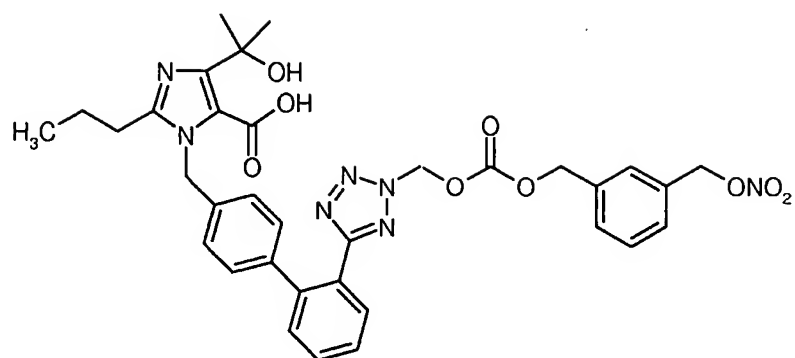


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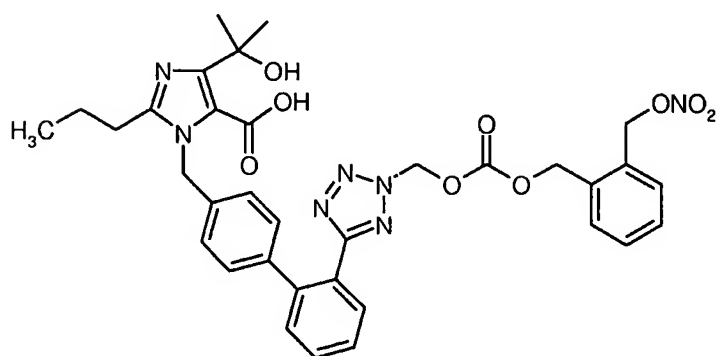
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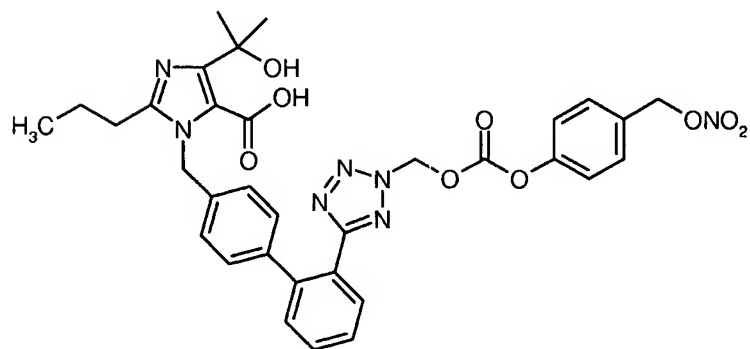
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(220)

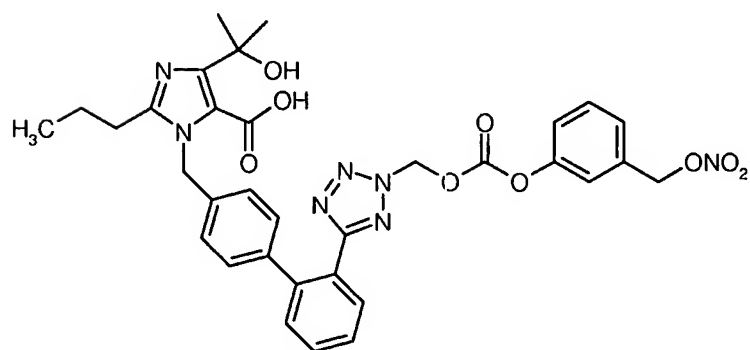


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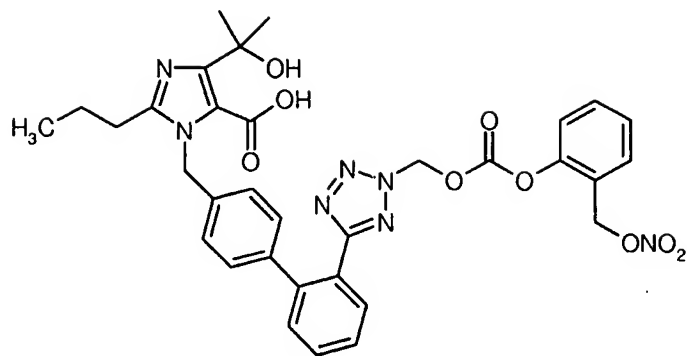
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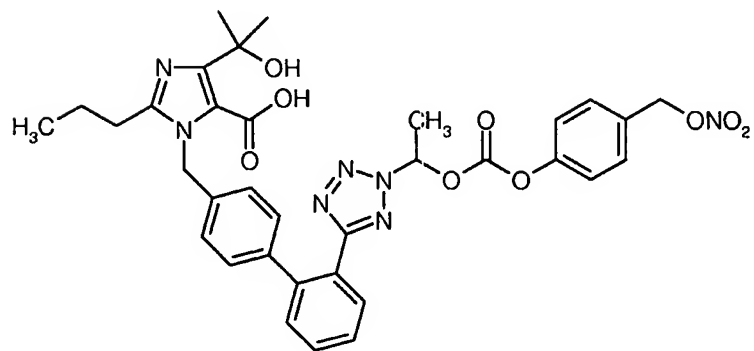


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(223)

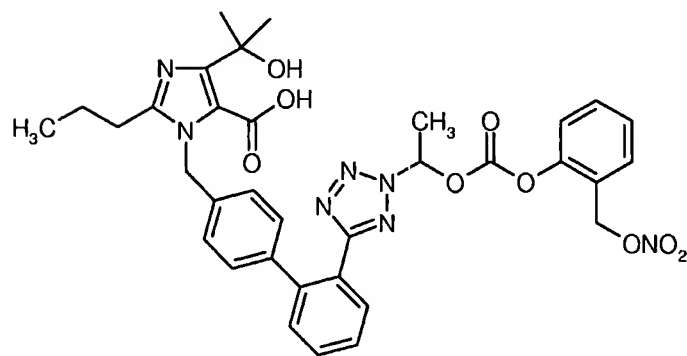


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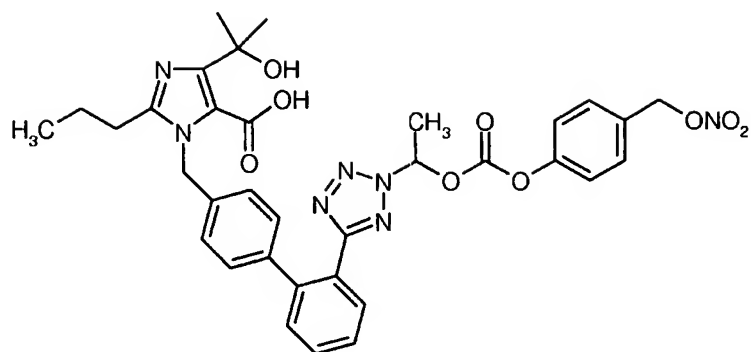


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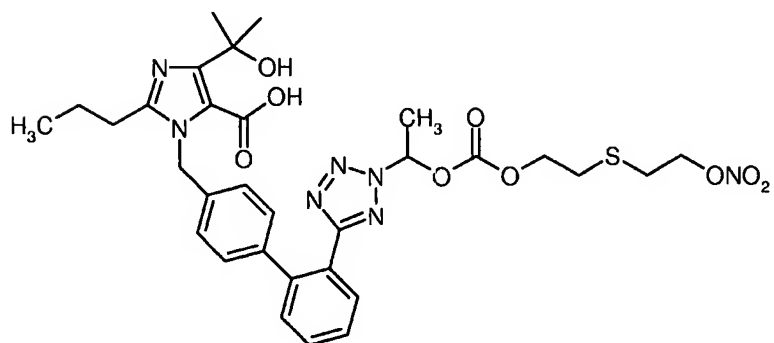
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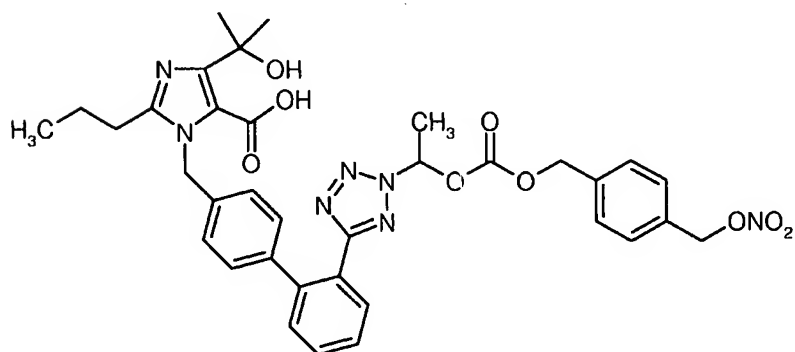
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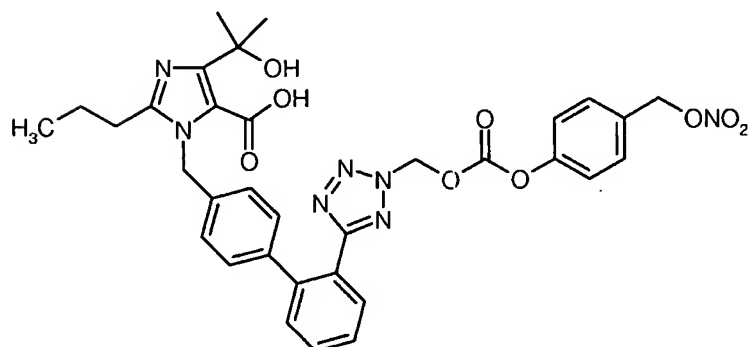
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(228)

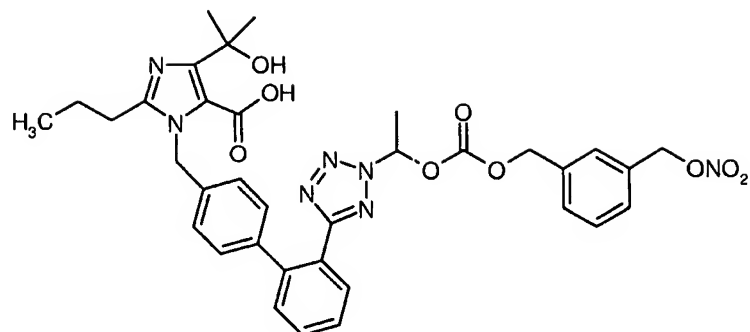


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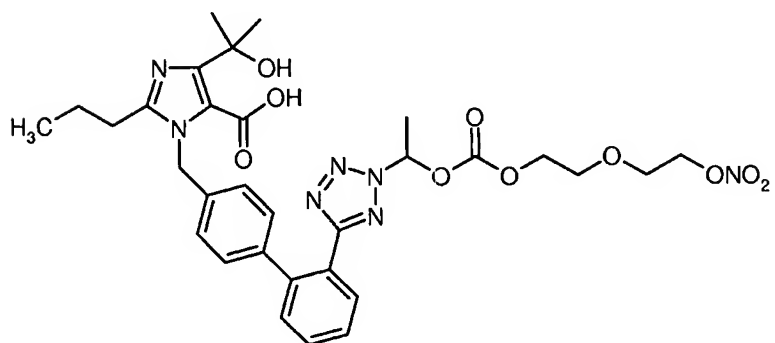


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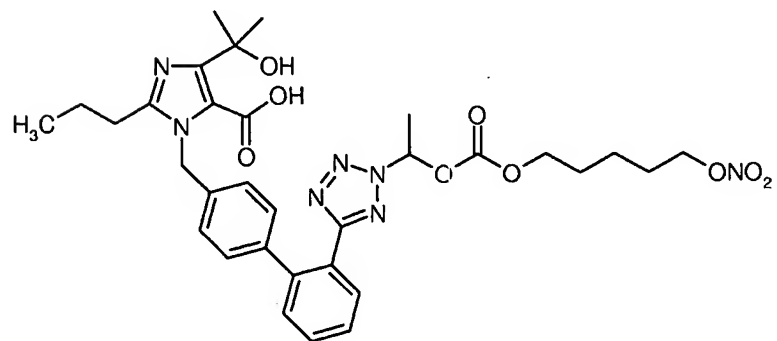
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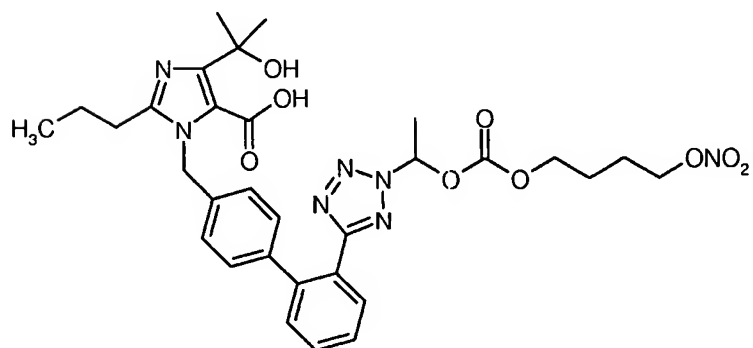
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(232)

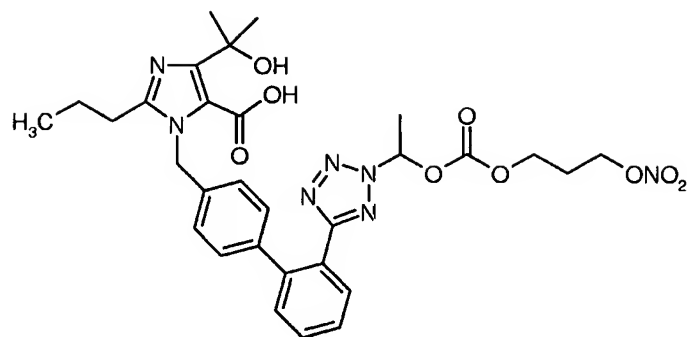


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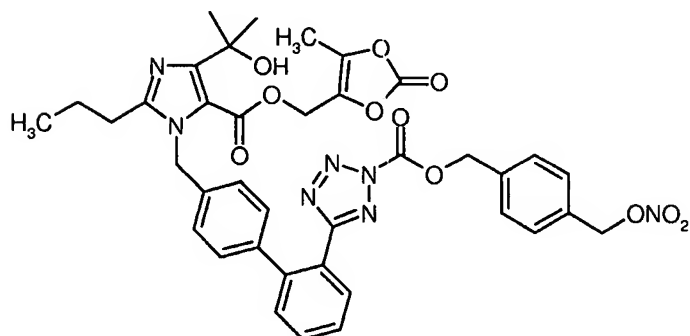


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(234)

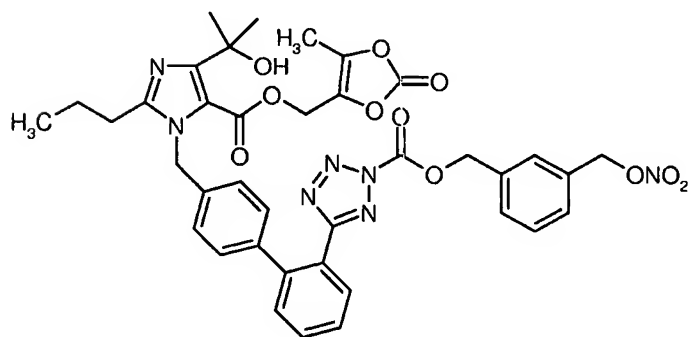


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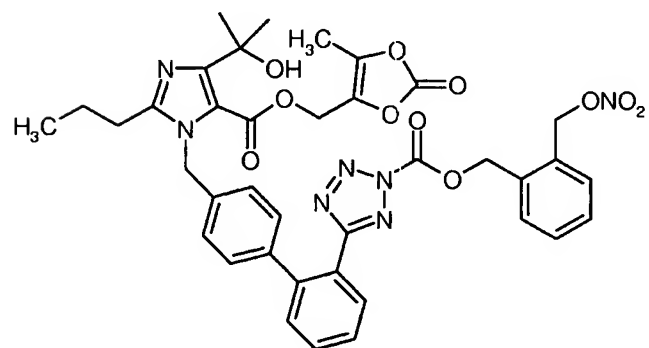


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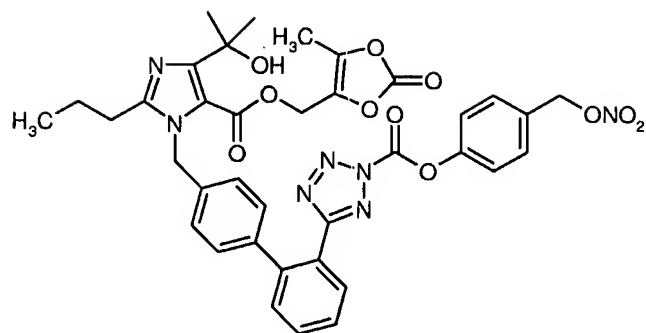
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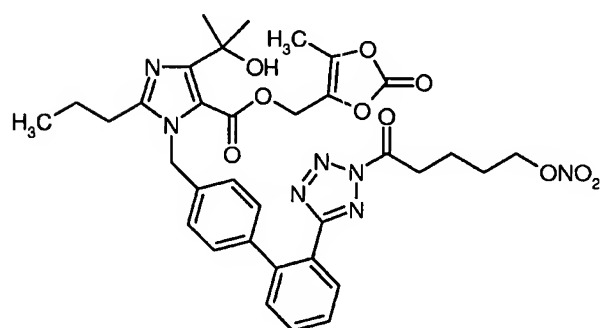
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(238)

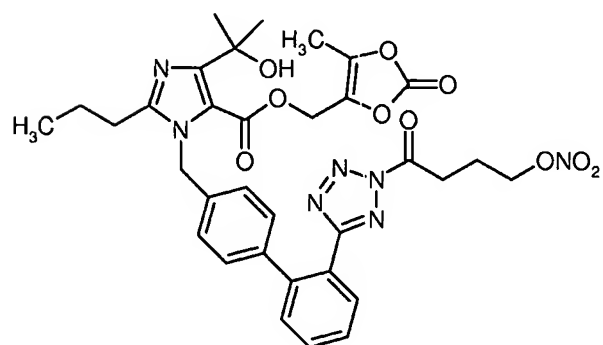


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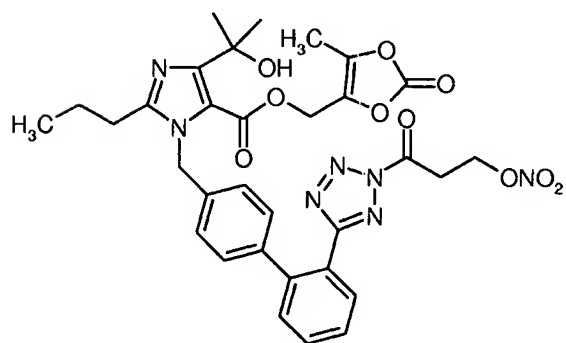


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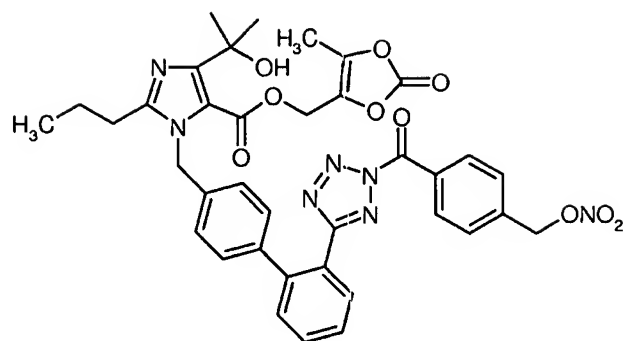
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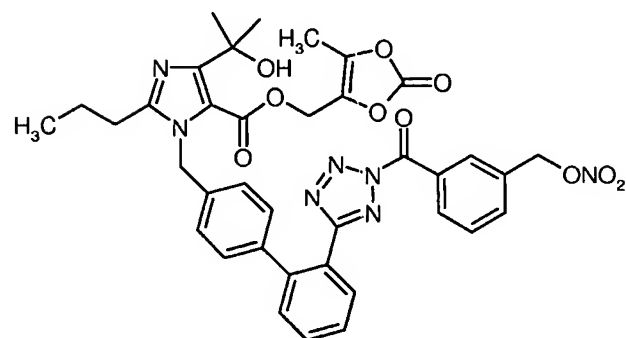
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(242)

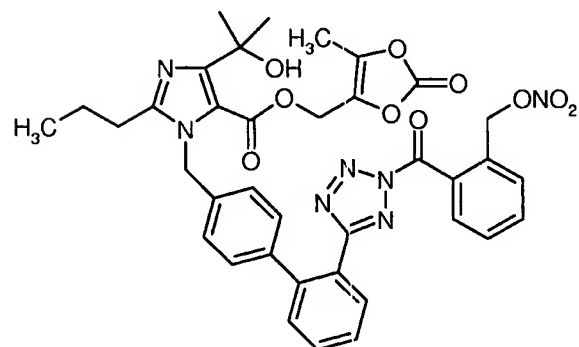


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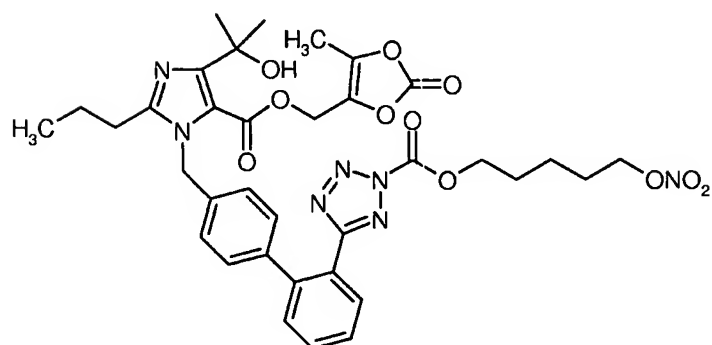


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(244)

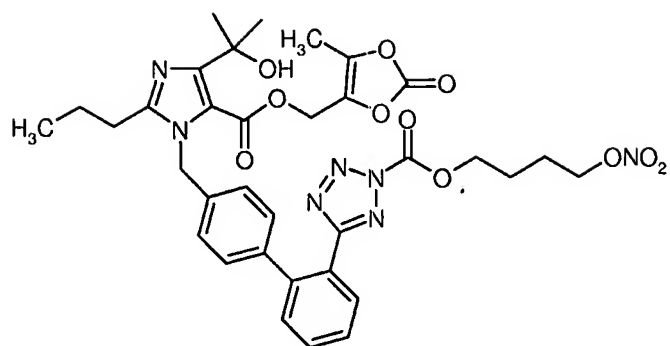


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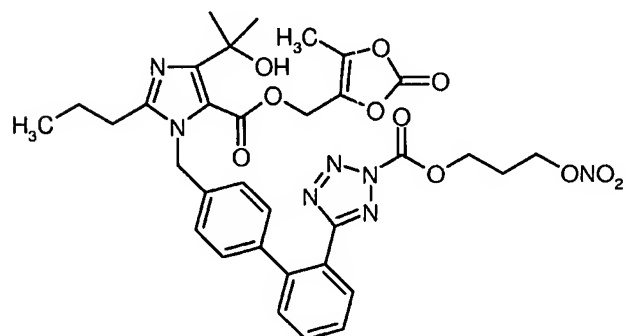


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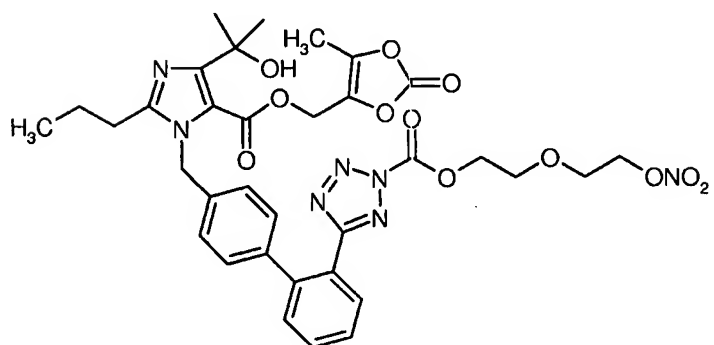
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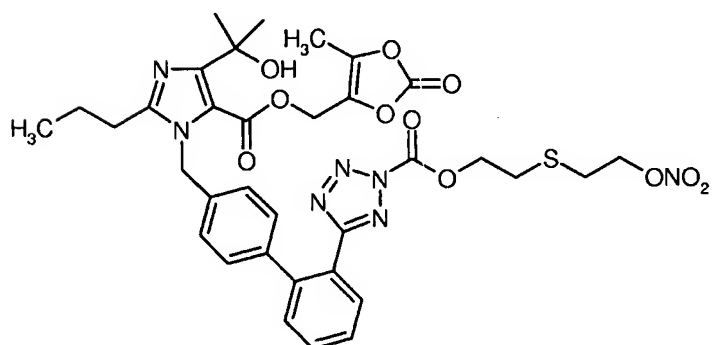
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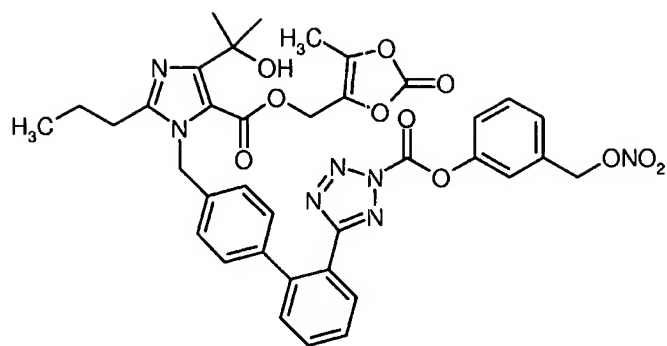
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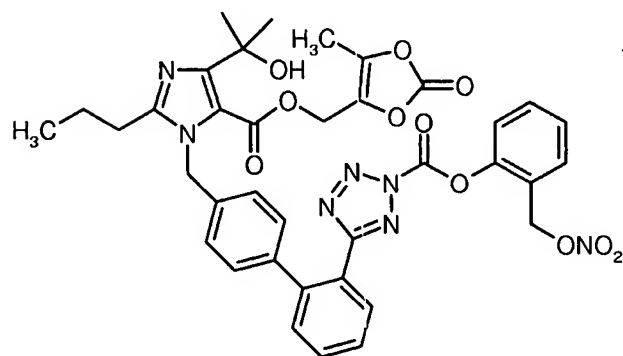
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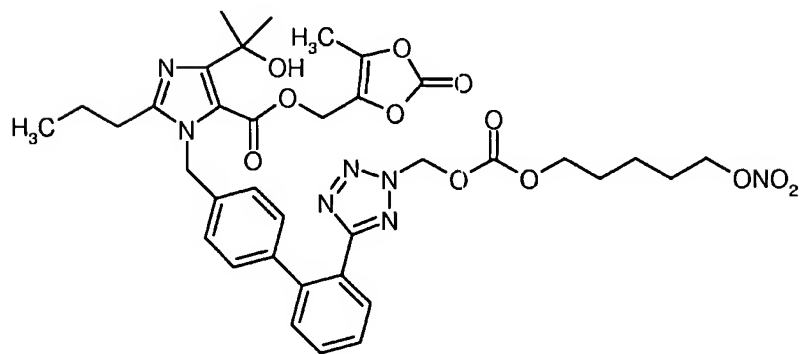


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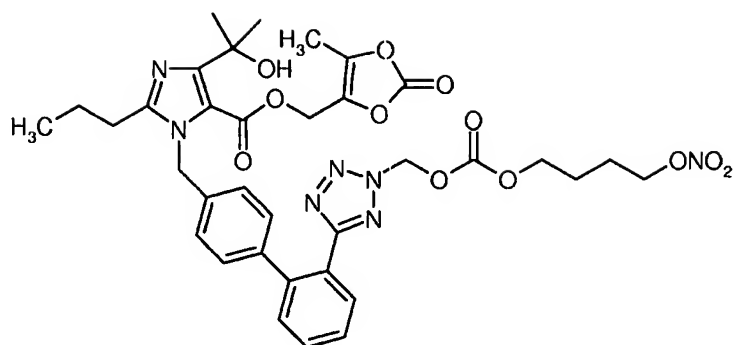


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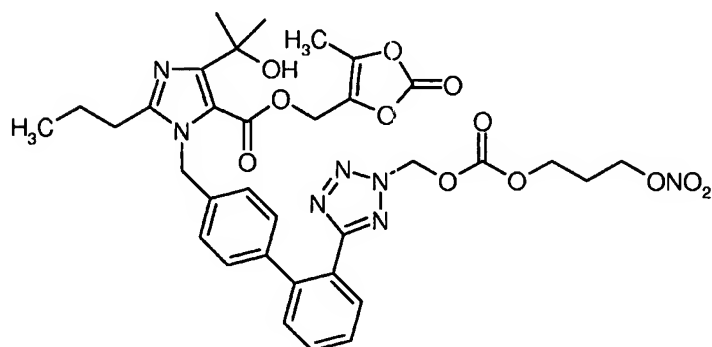
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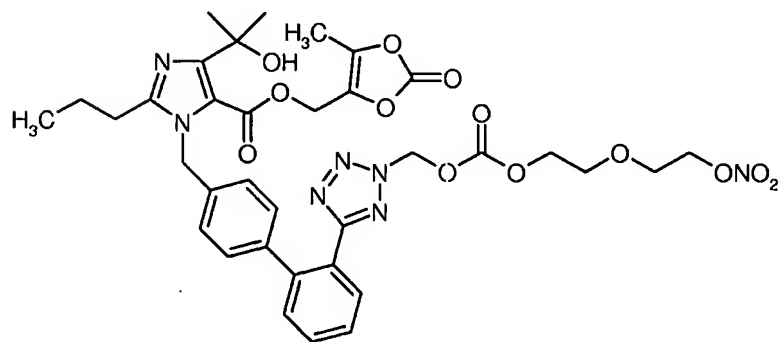
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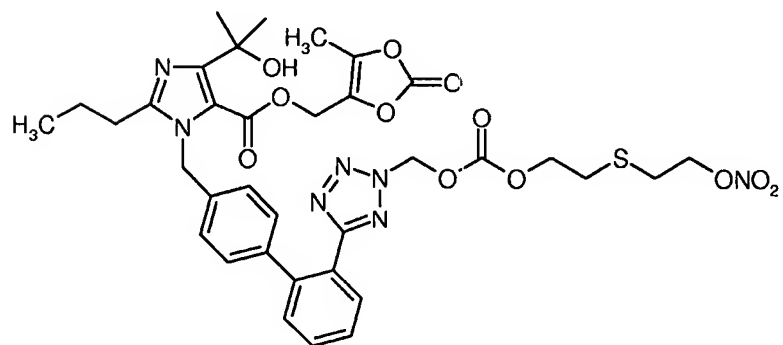
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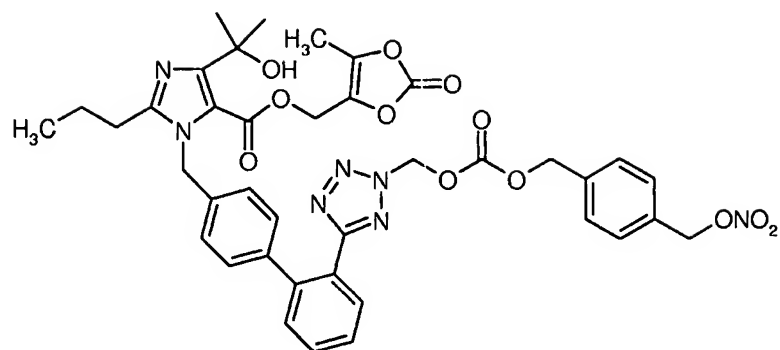
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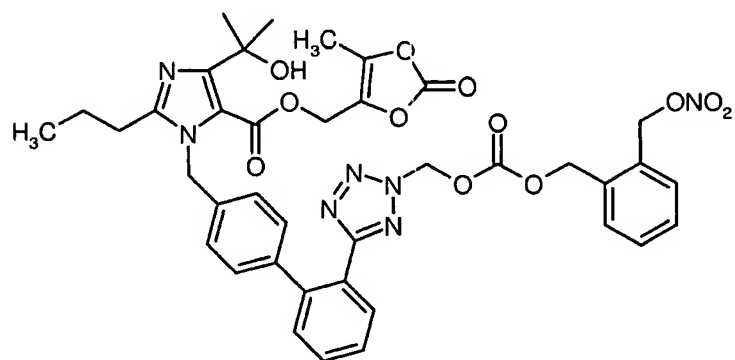
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(257)

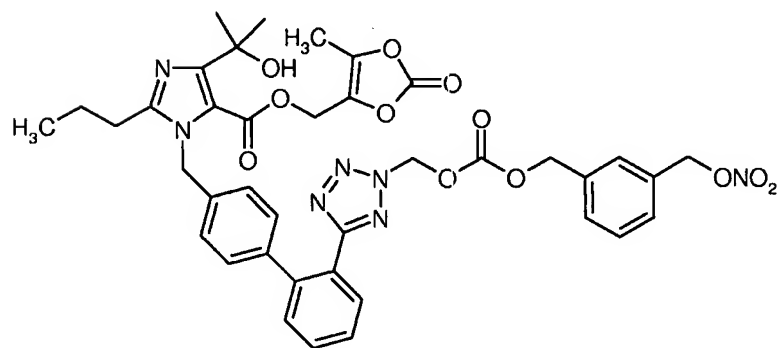


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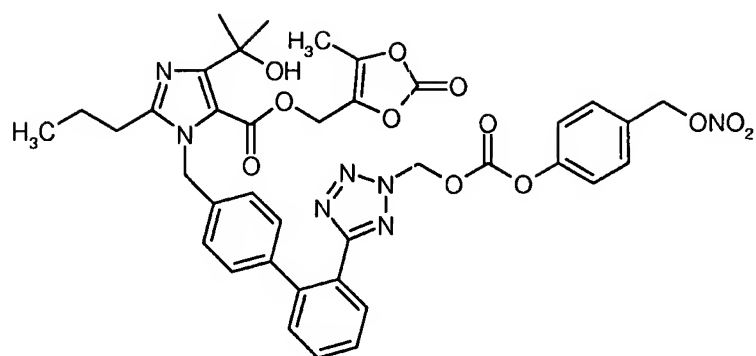


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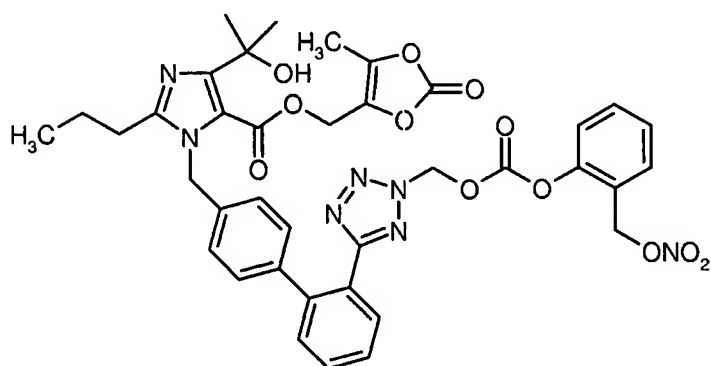
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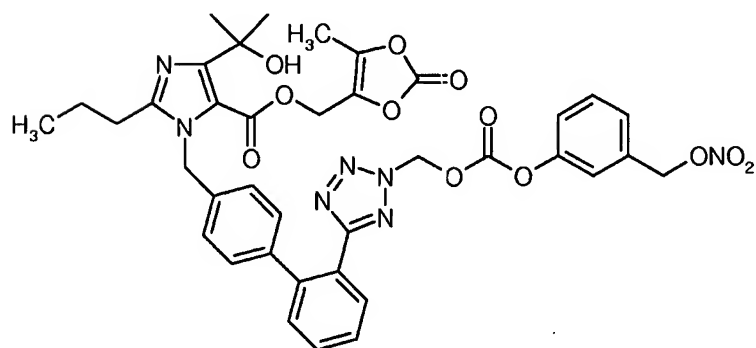
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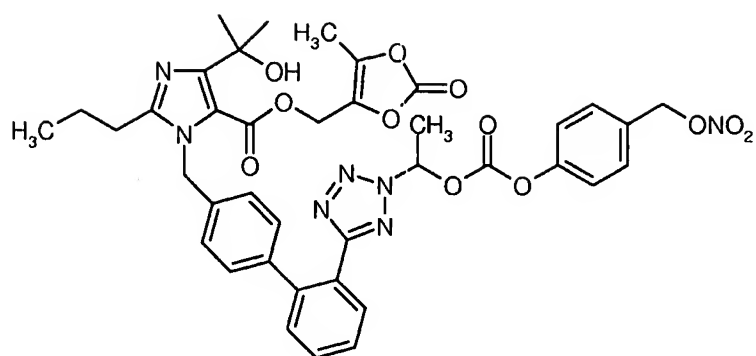
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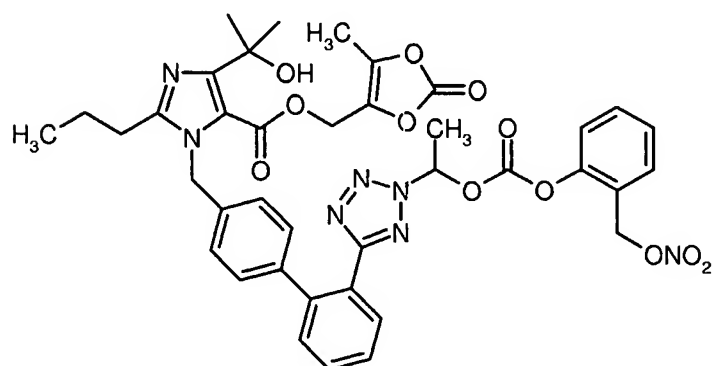
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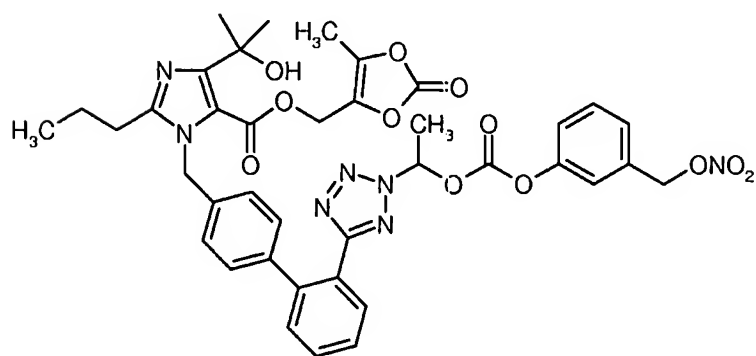
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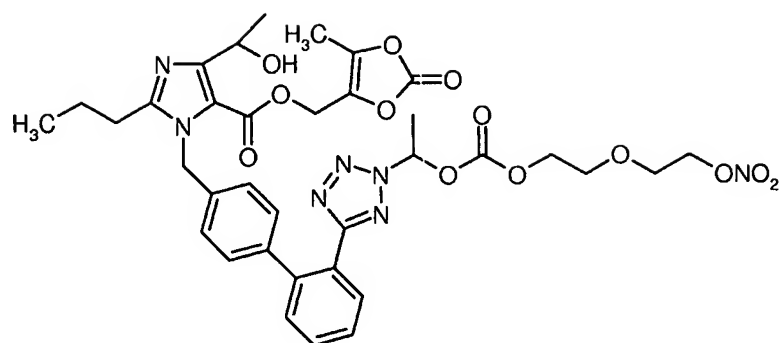
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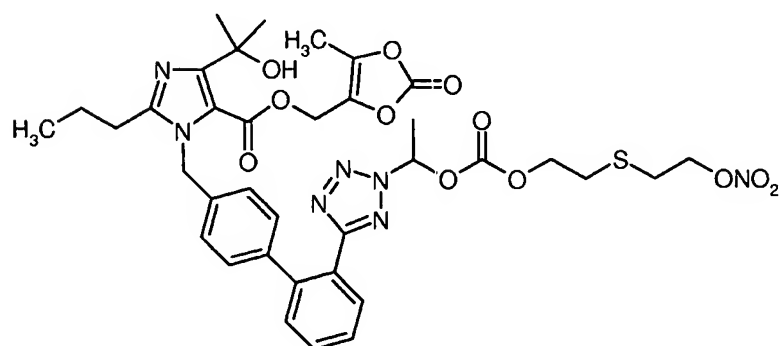
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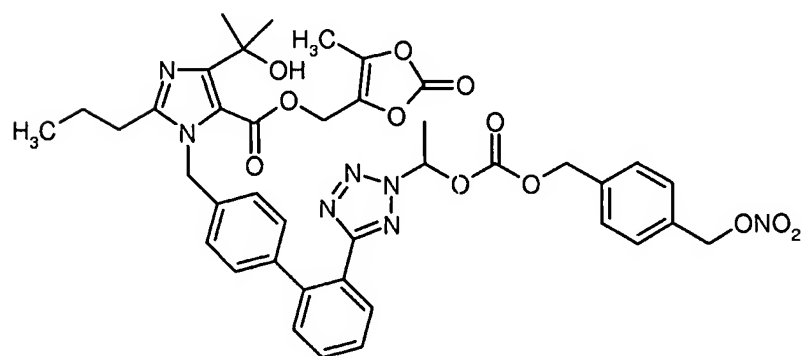
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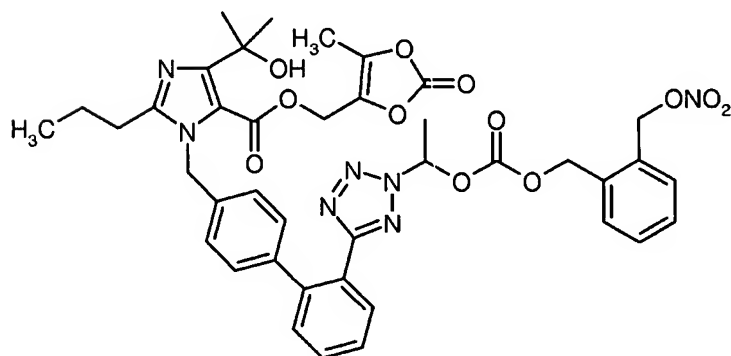
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(268)

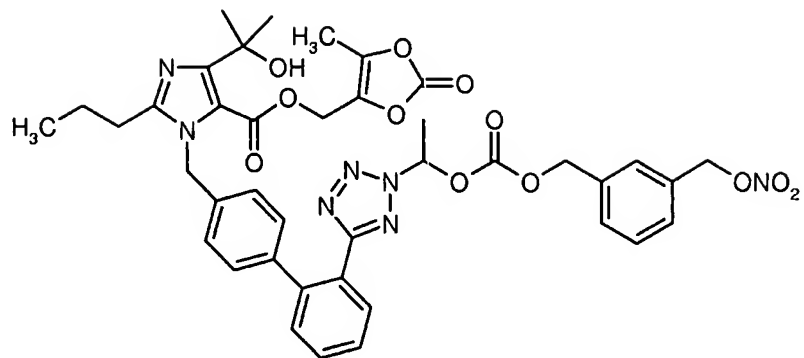


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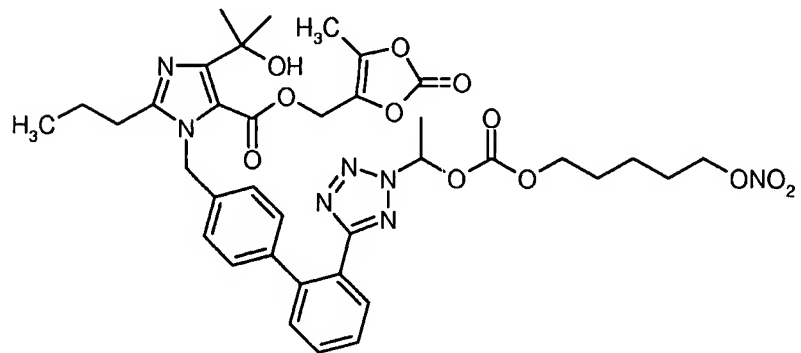


273

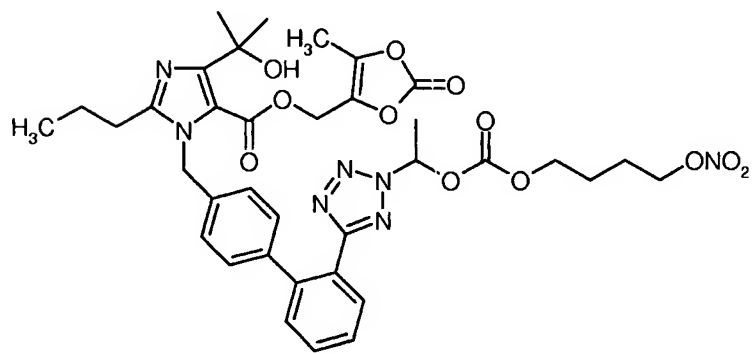
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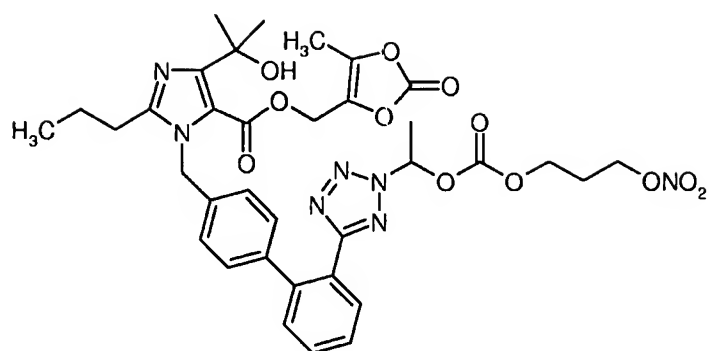
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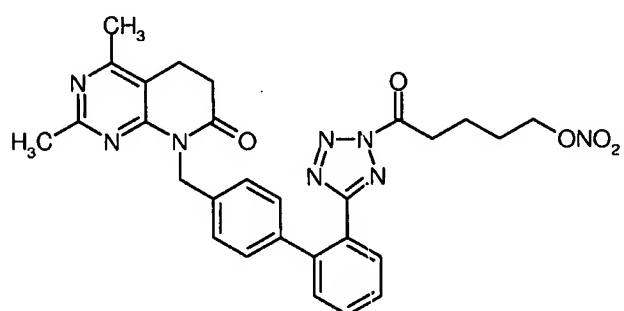
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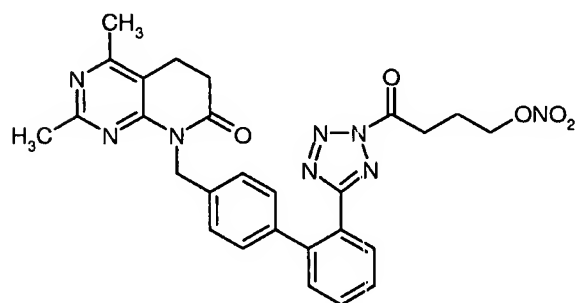
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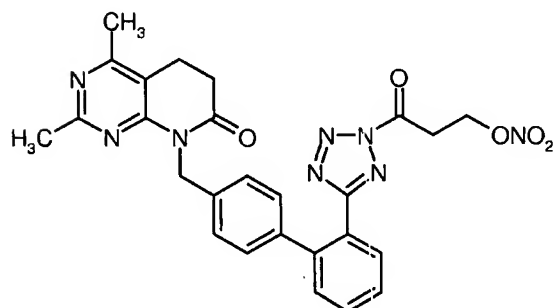
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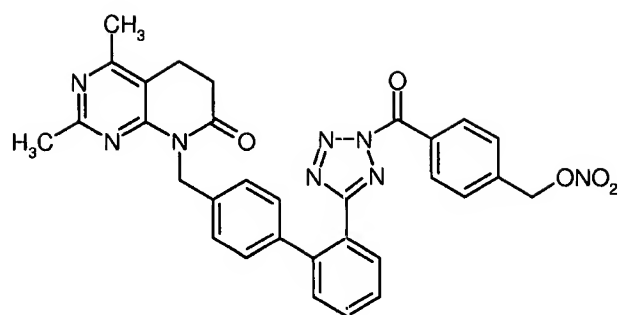
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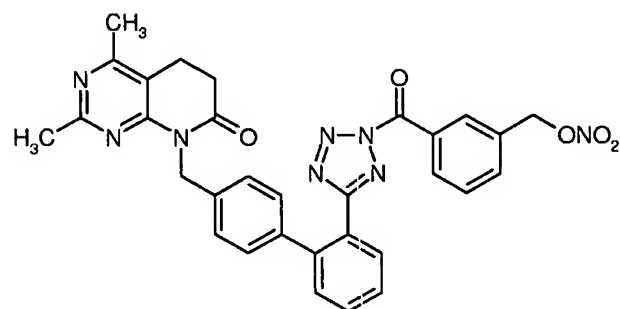
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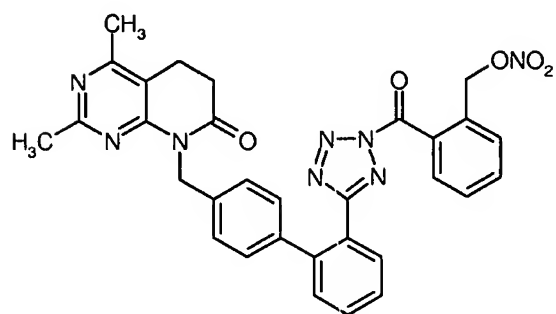
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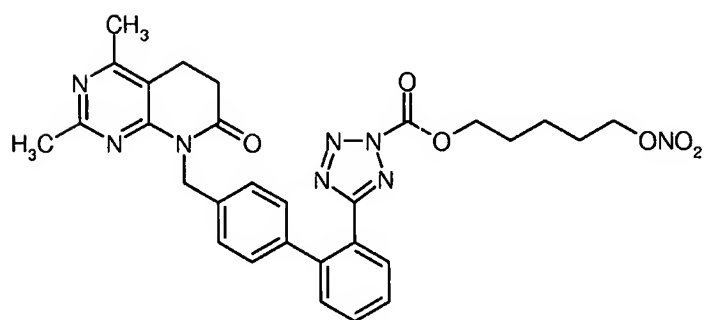
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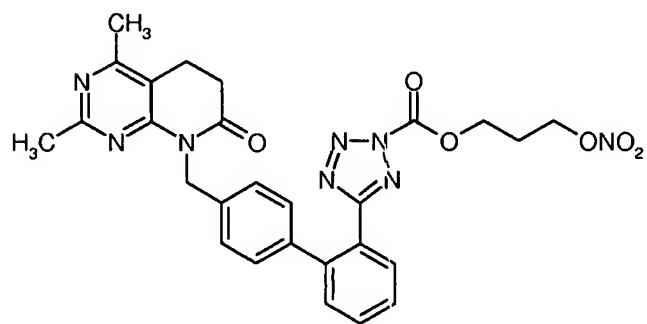
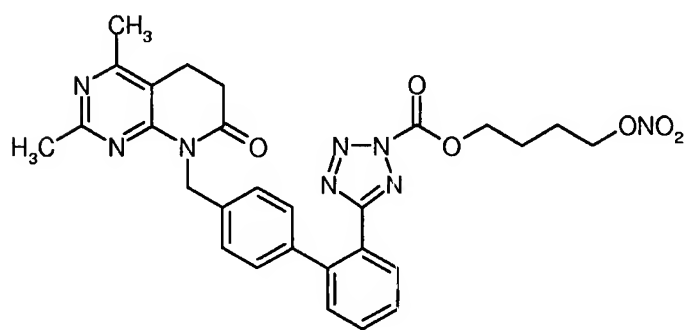
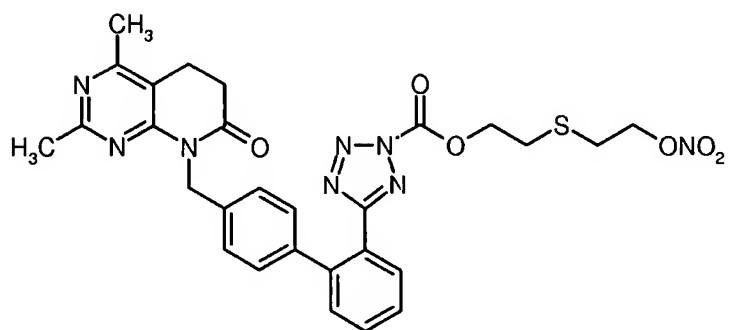
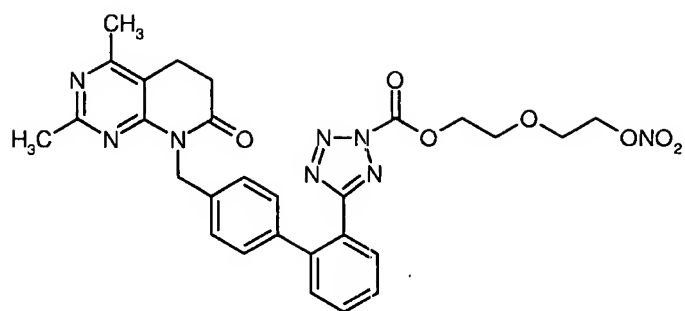
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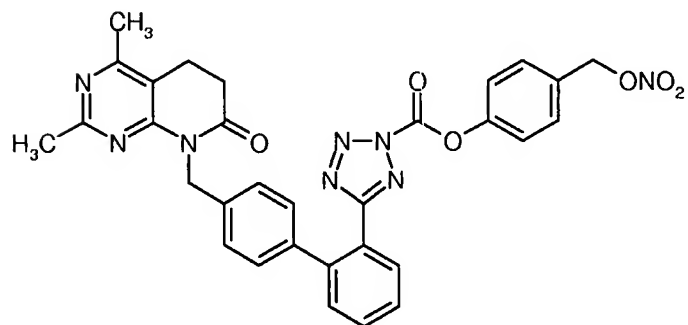
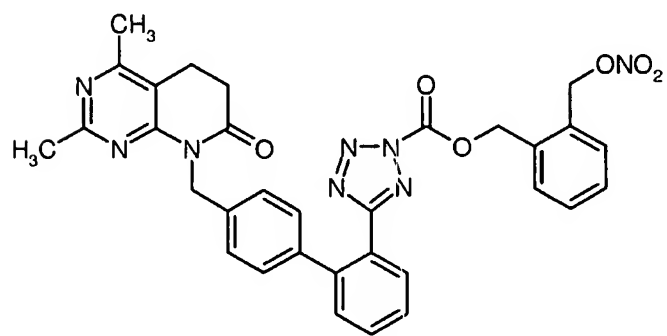
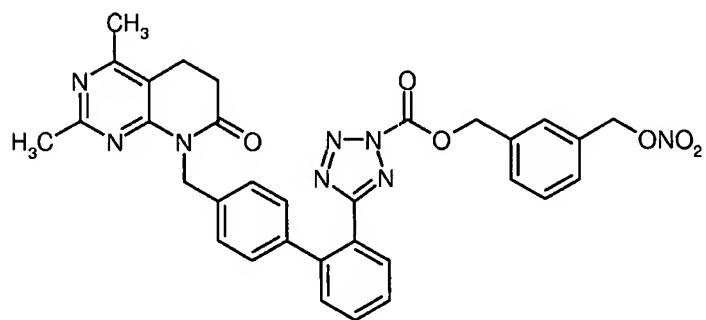
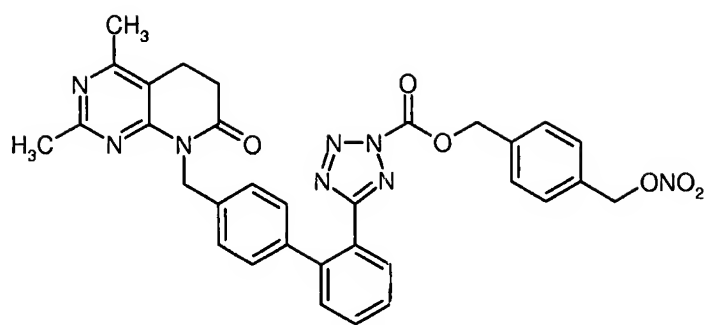


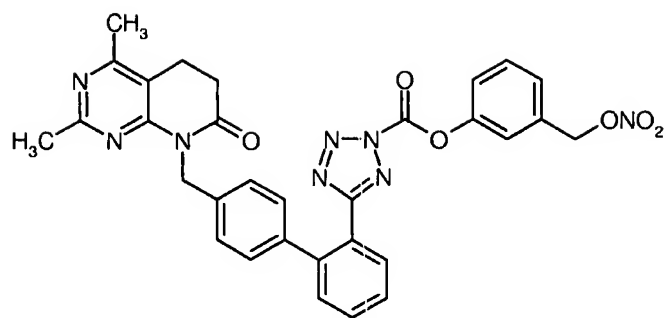
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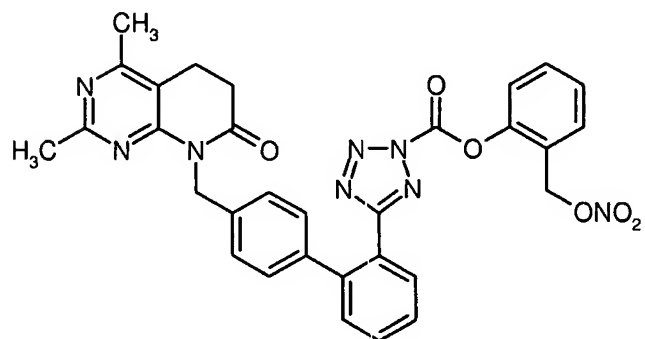
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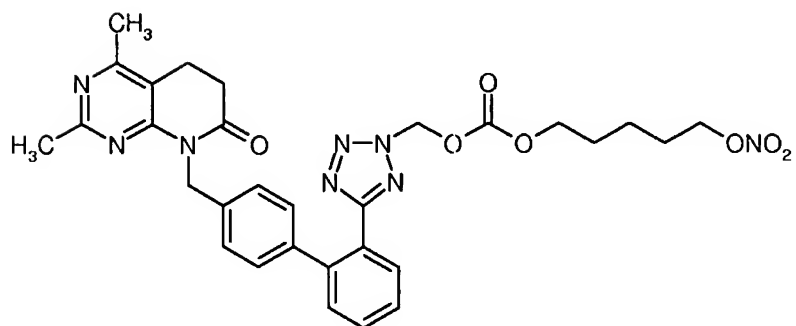




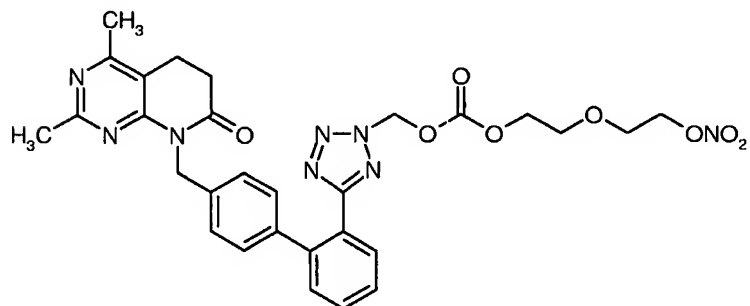
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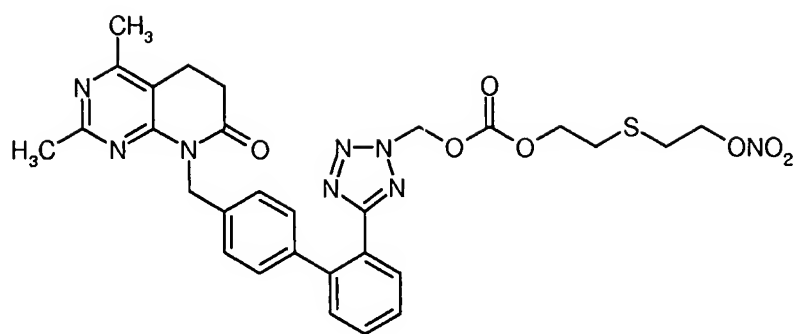
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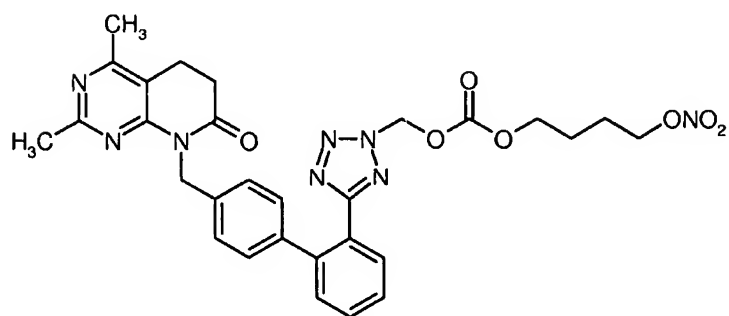
(292)



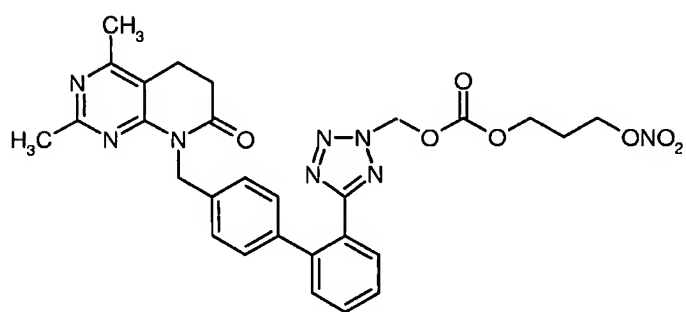
(293)



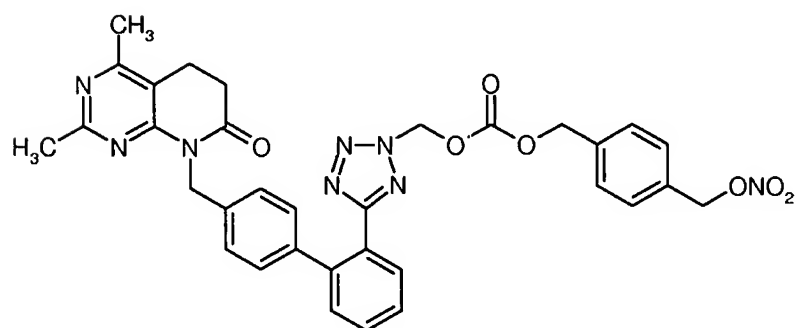
(294)



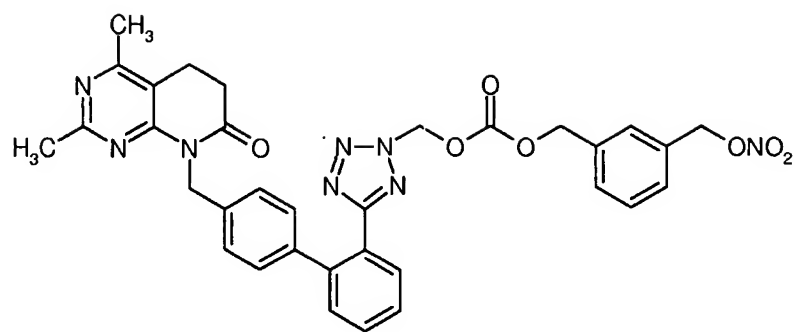
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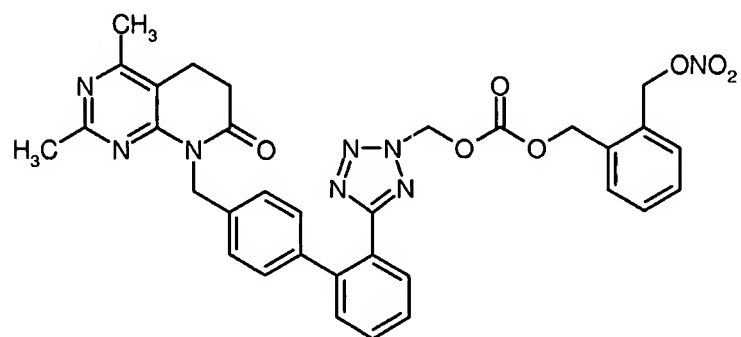
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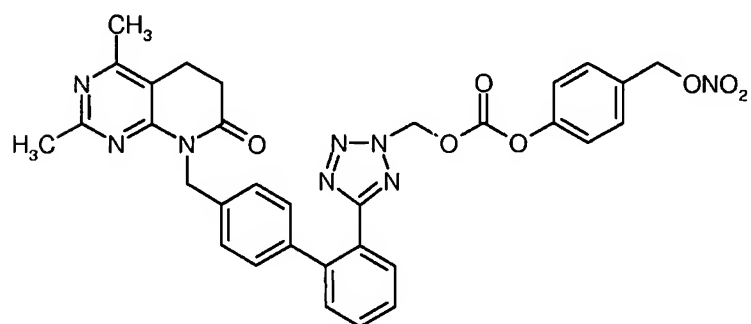
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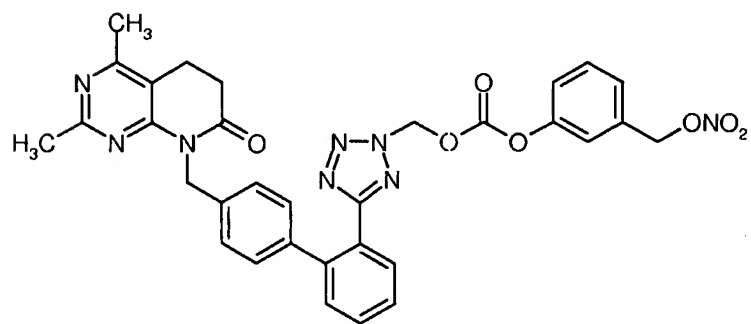
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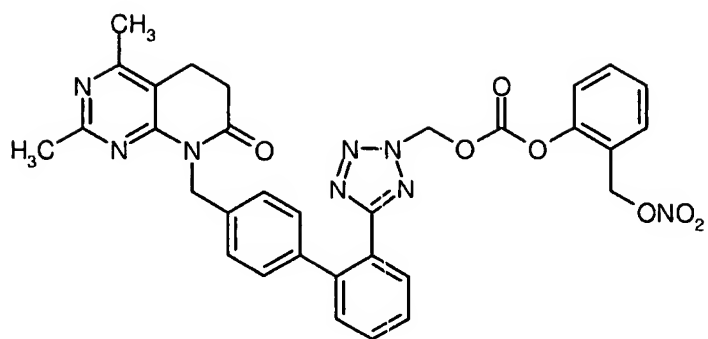
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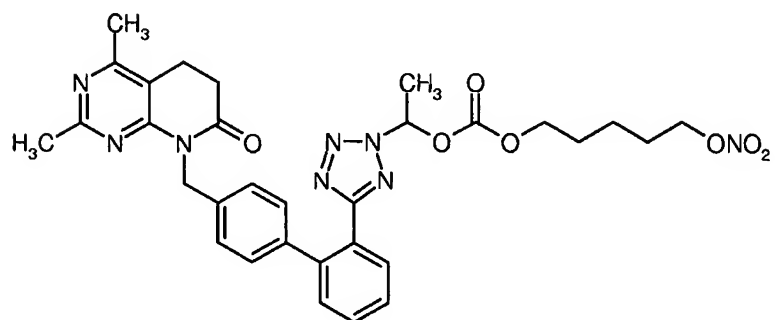
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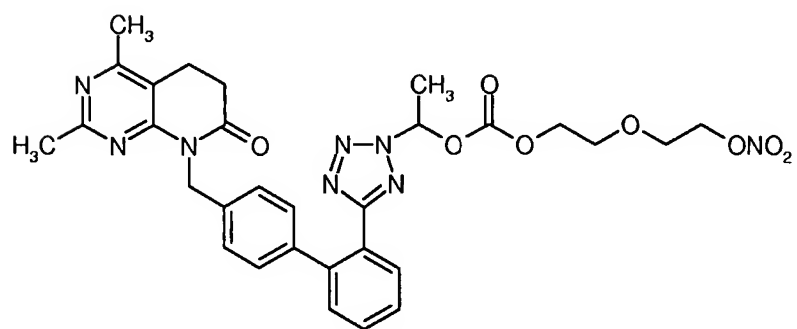
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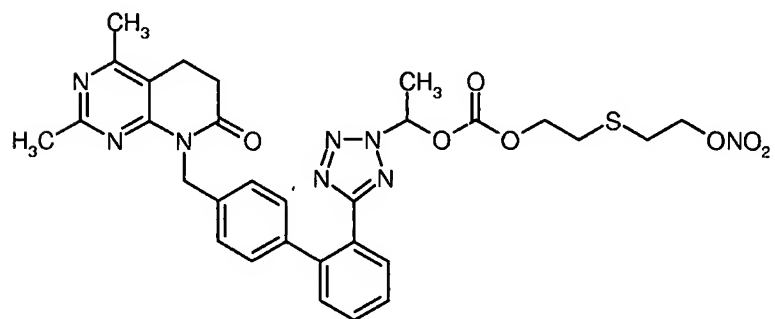
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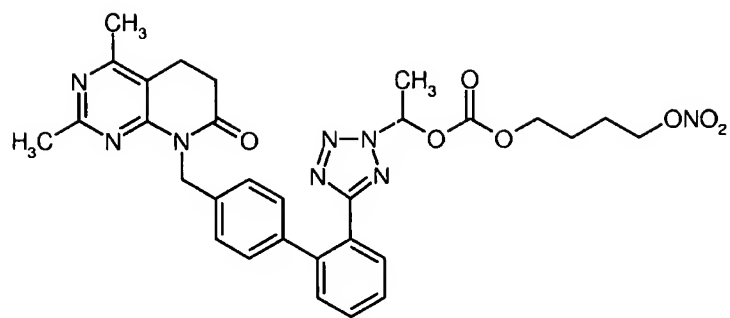
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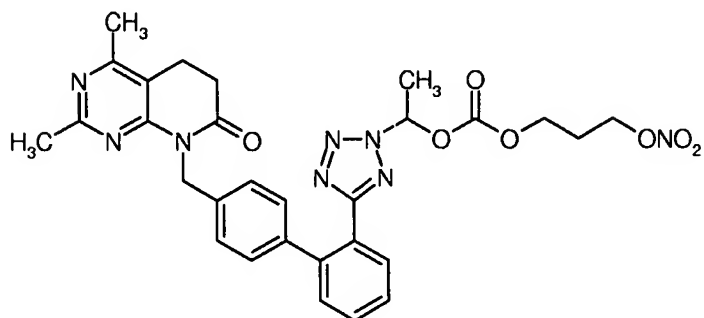
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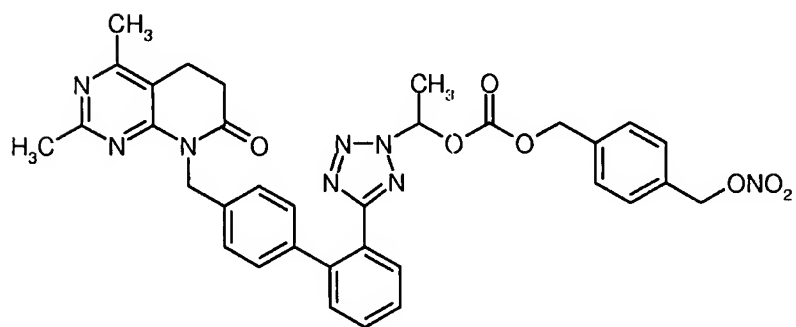
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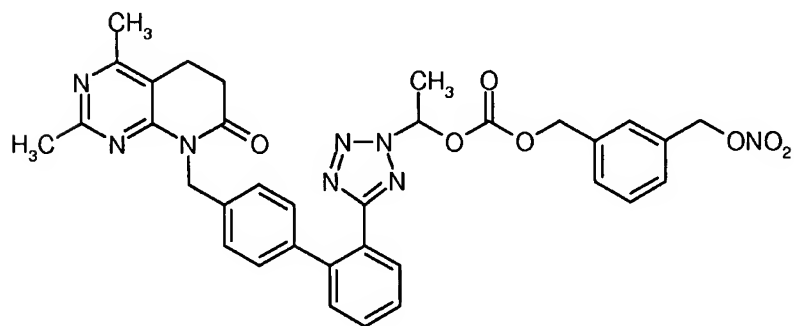
(306)



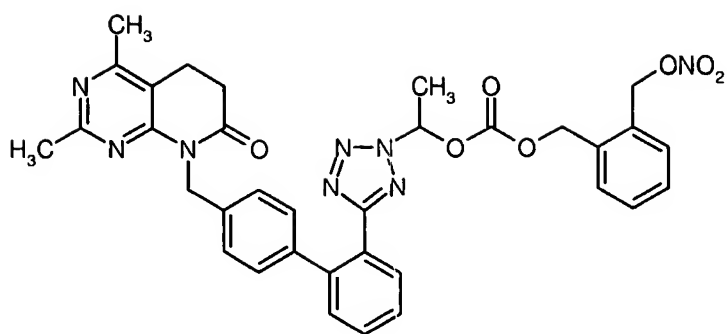
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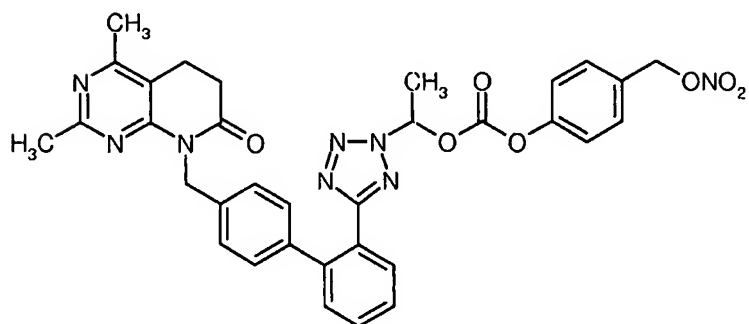
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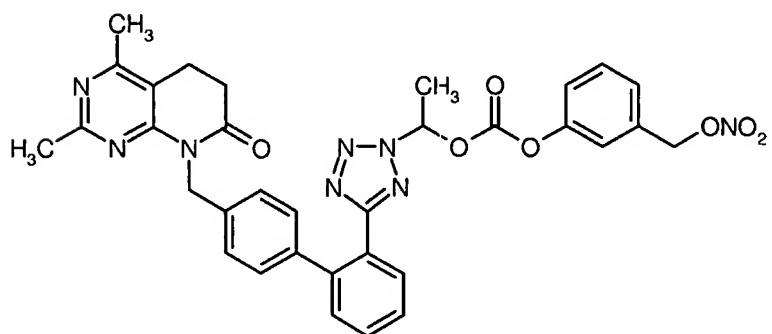
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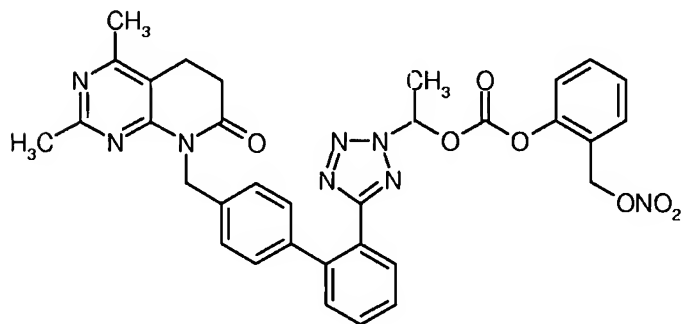
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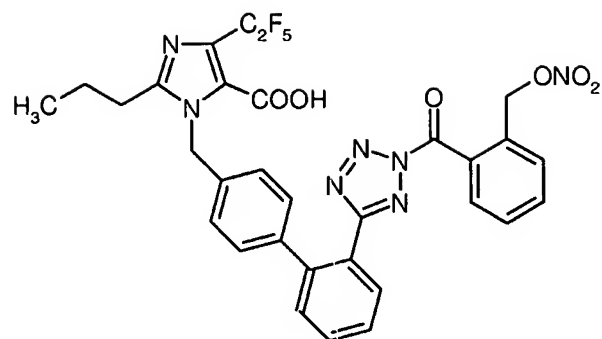
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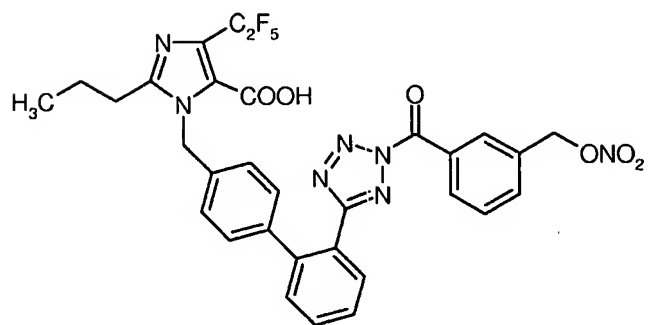
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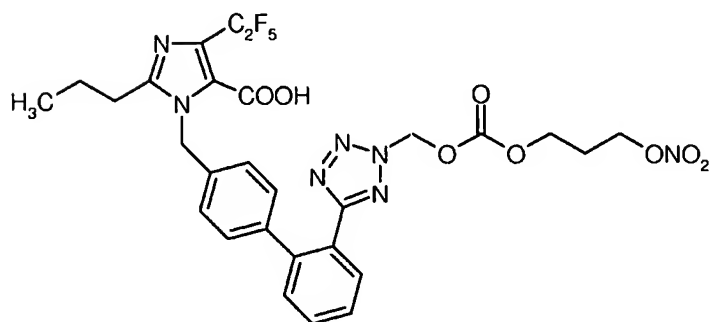
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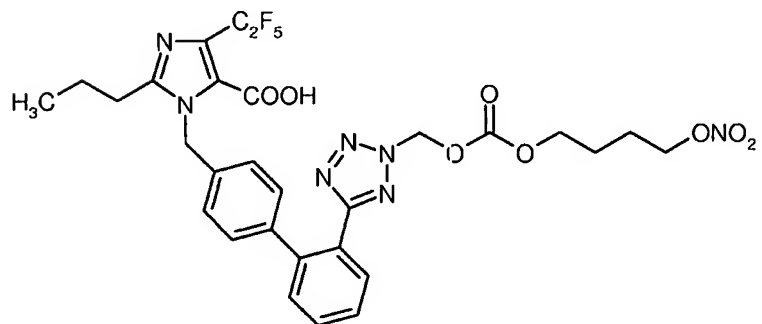
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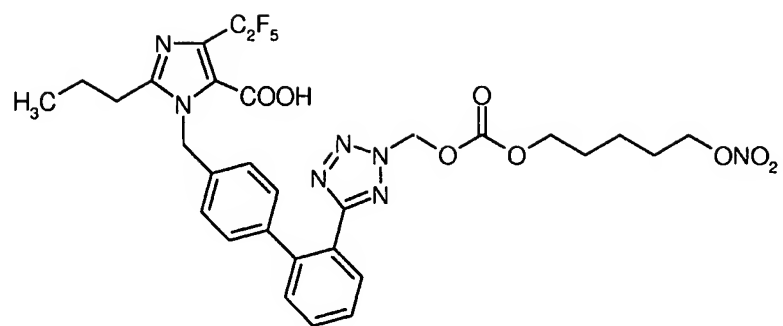
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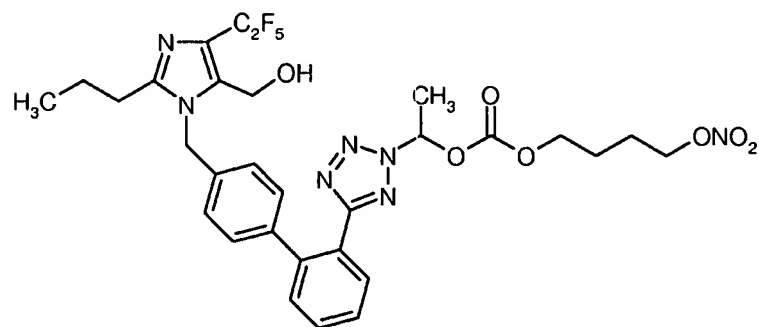
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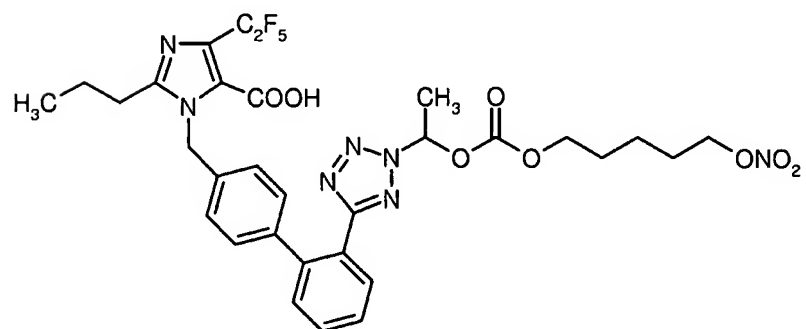
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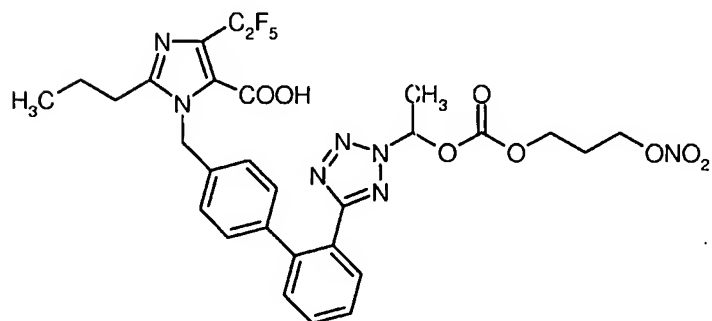
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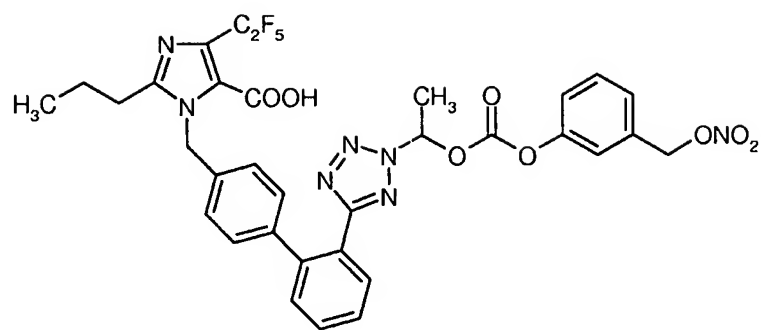
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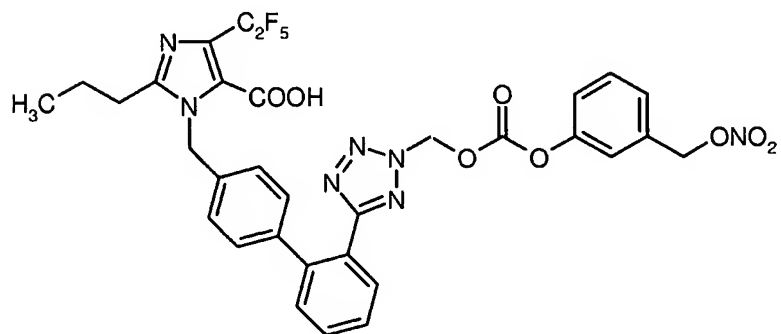
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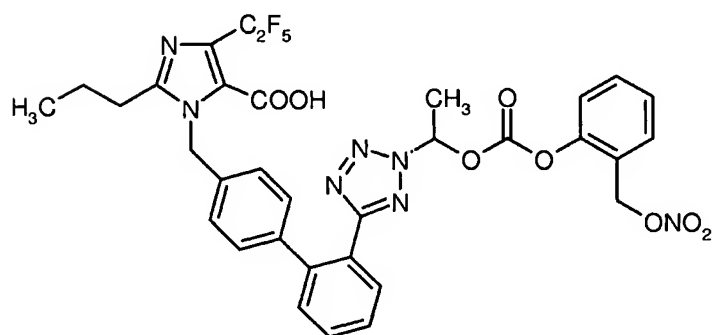
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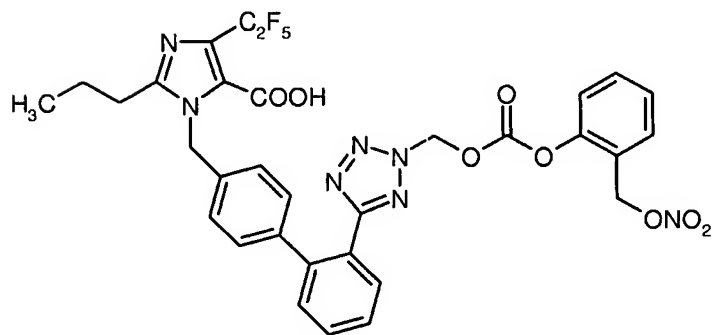
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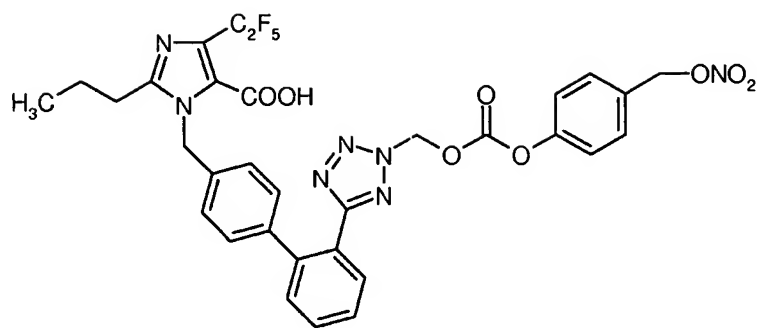
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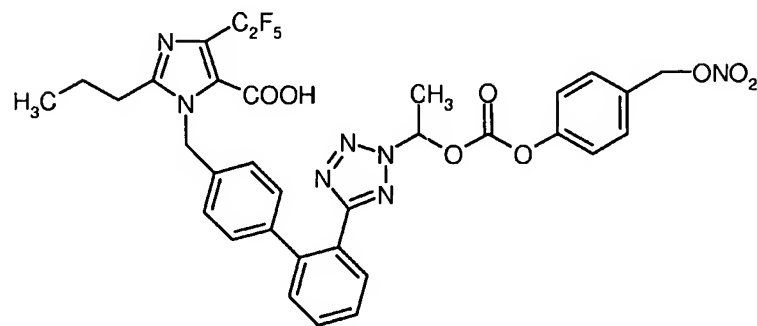
(328)



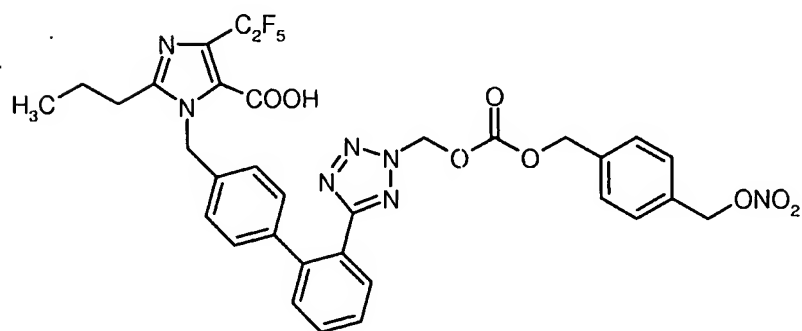
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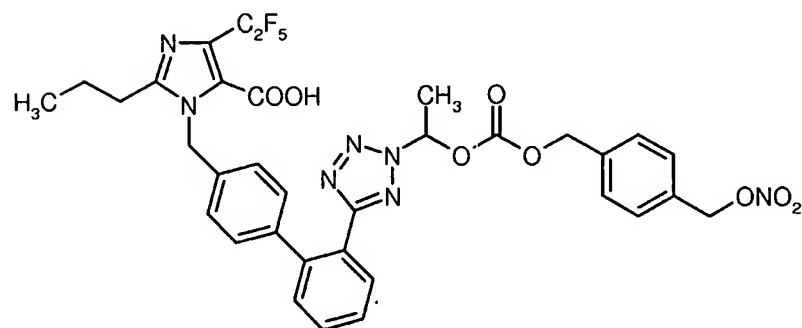
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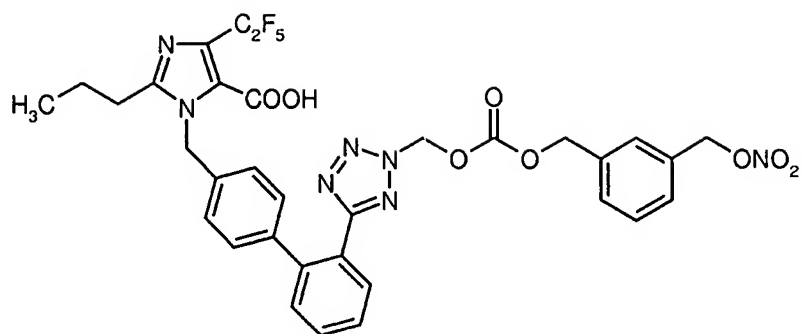
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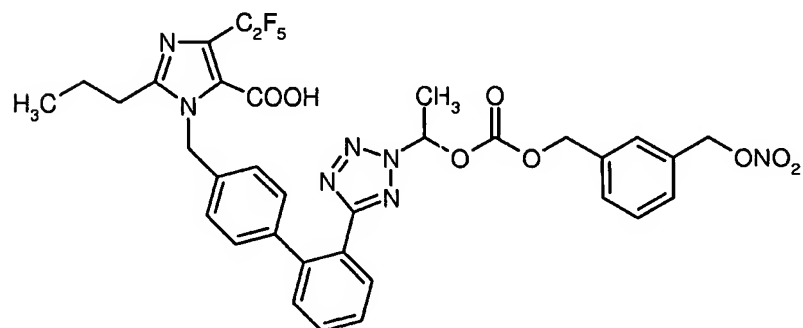
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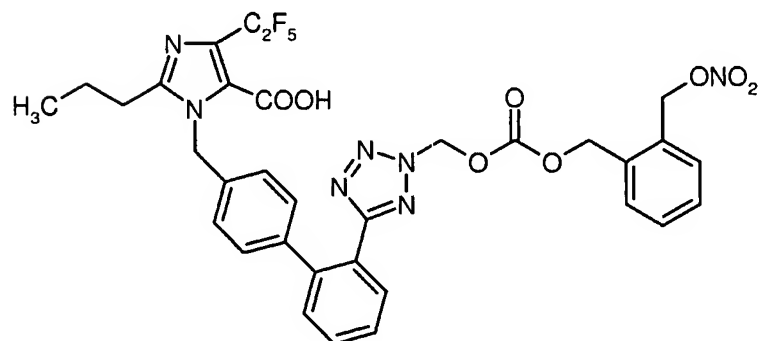
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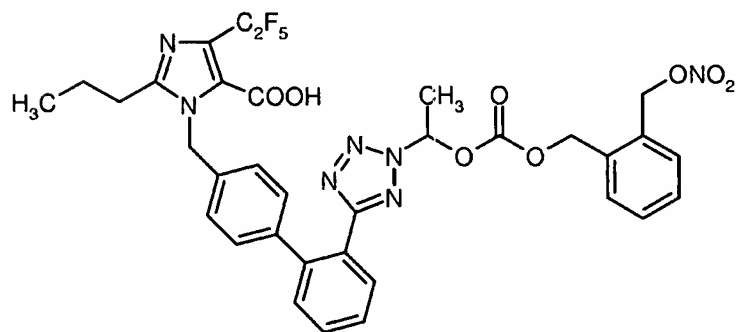
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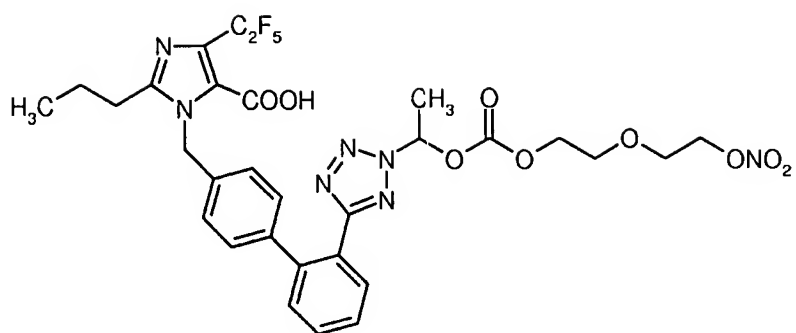
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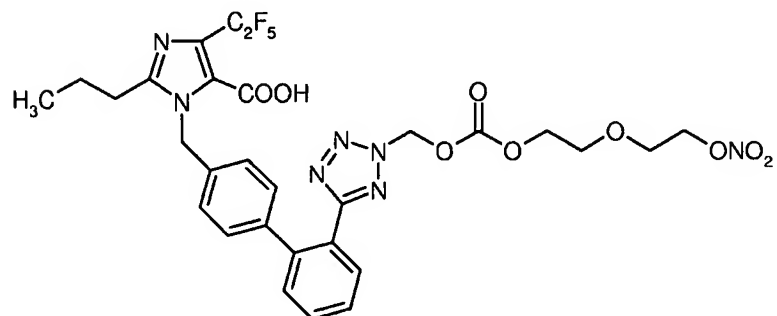
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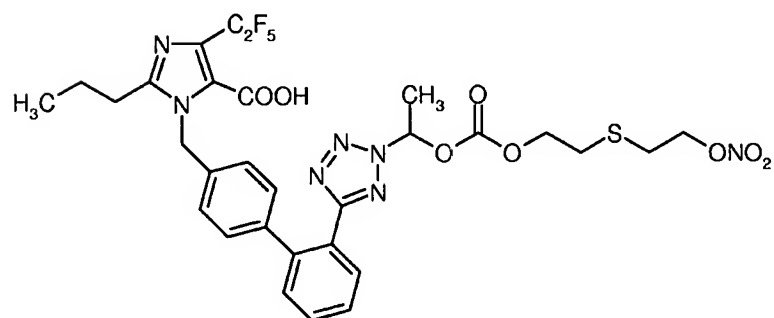
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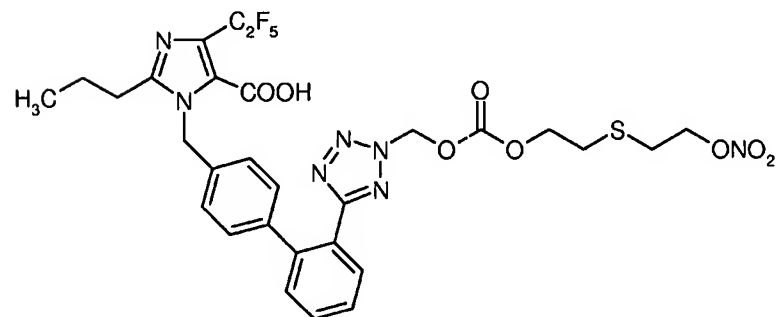
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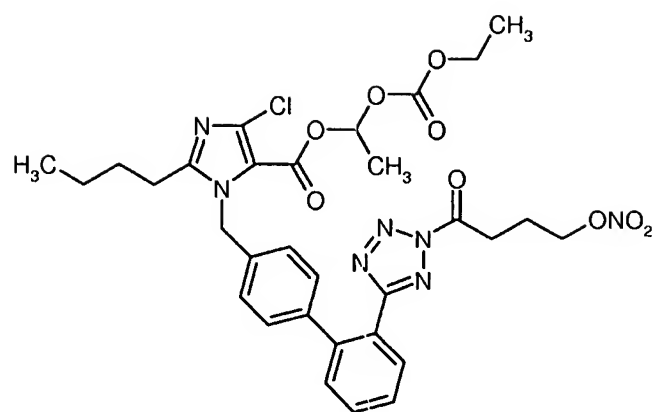
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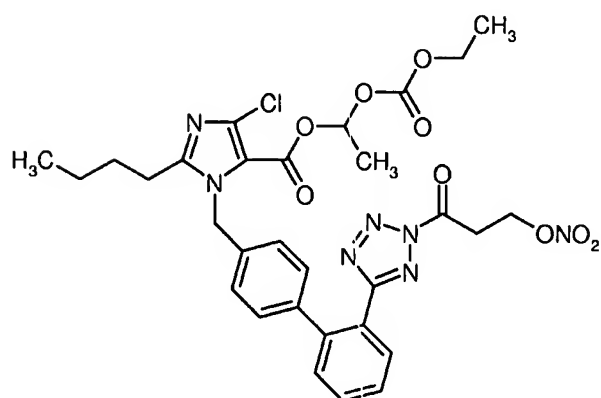
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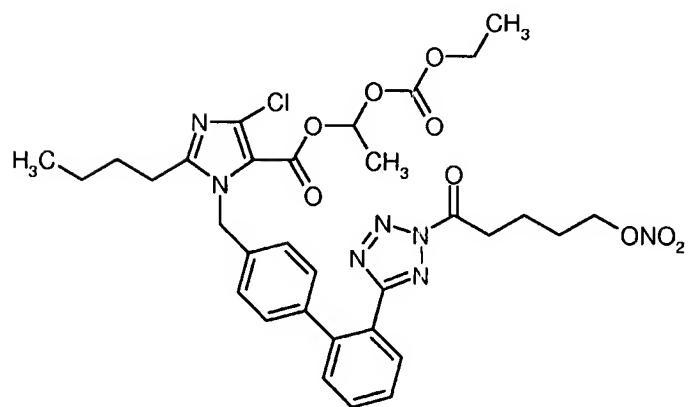
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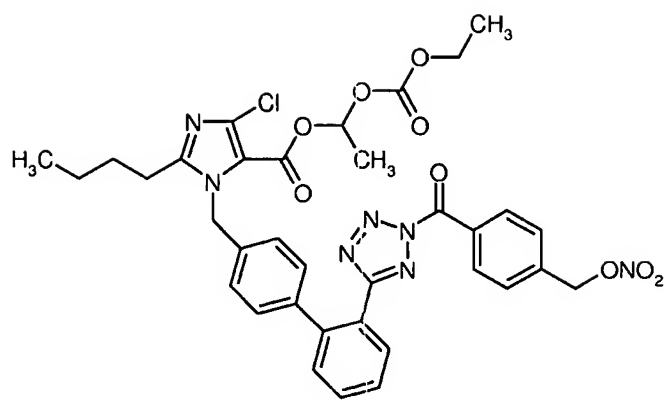
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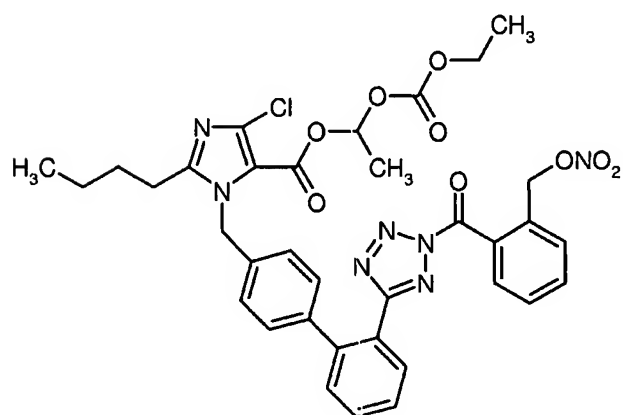
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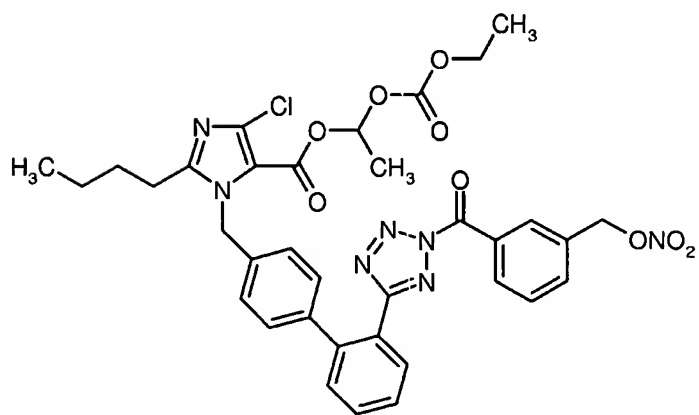
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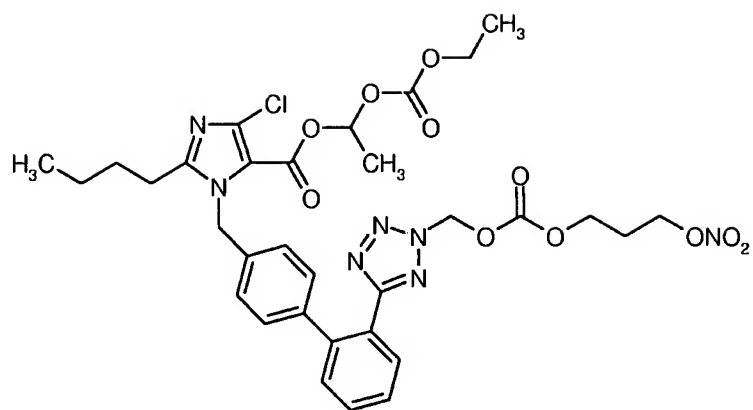
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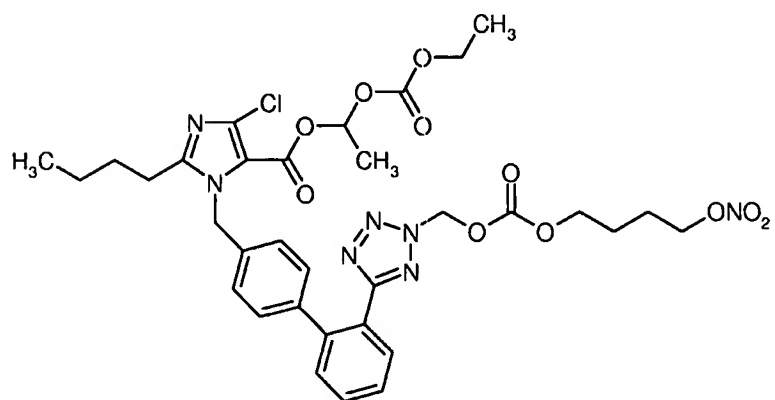
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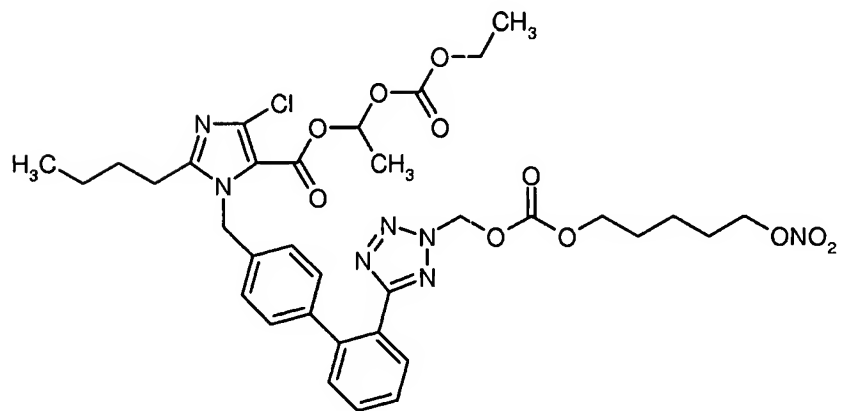
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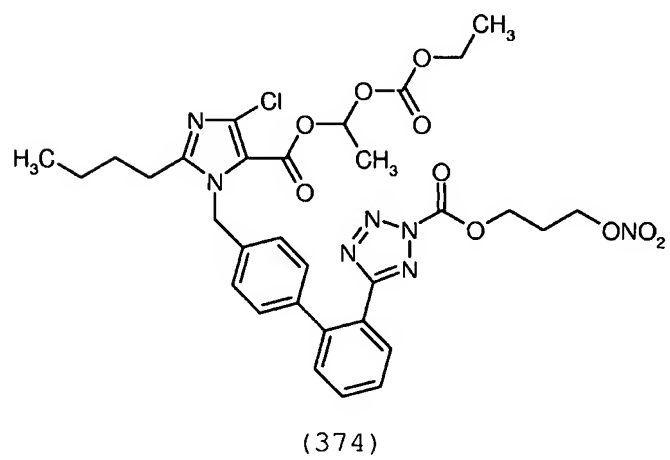
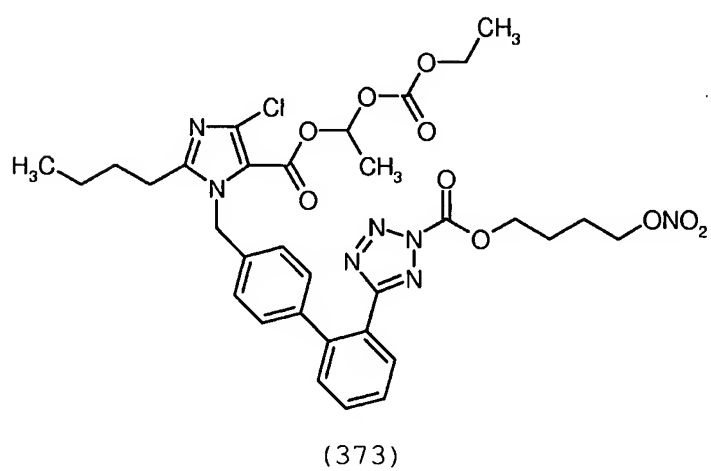
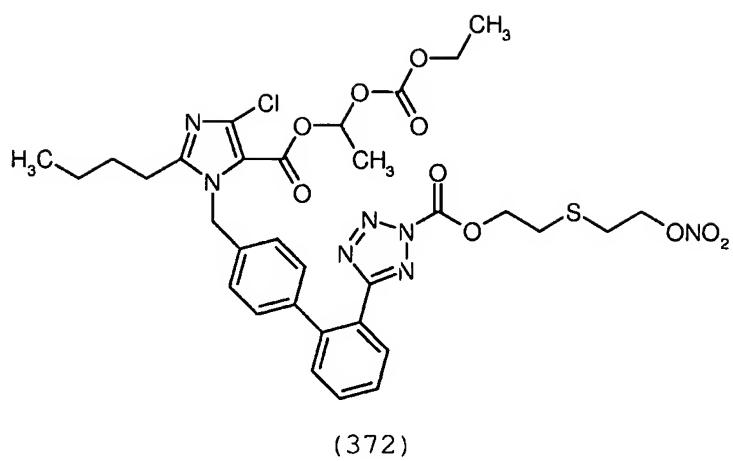
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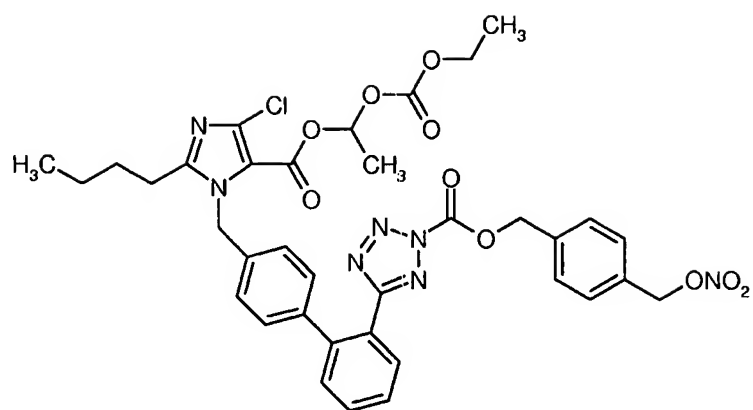


(349)

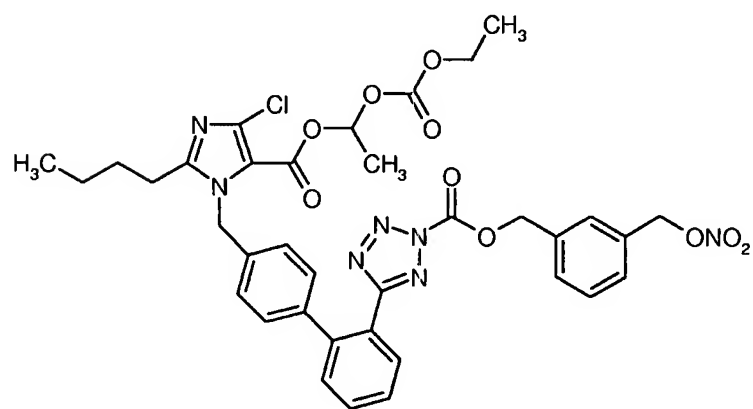


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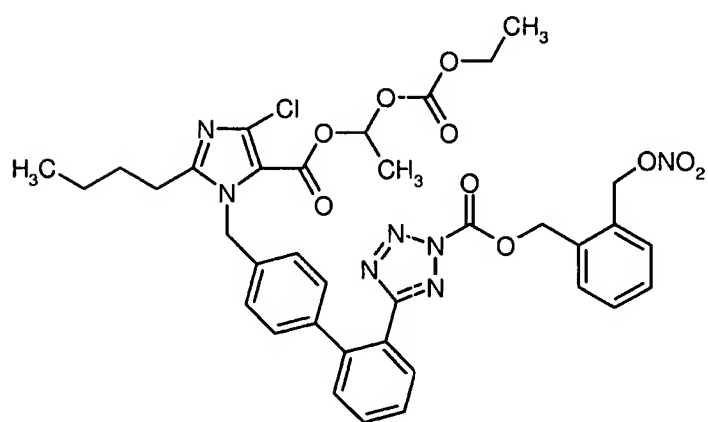




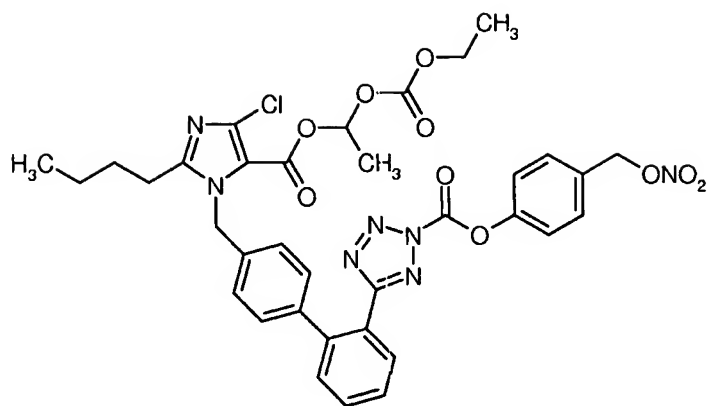
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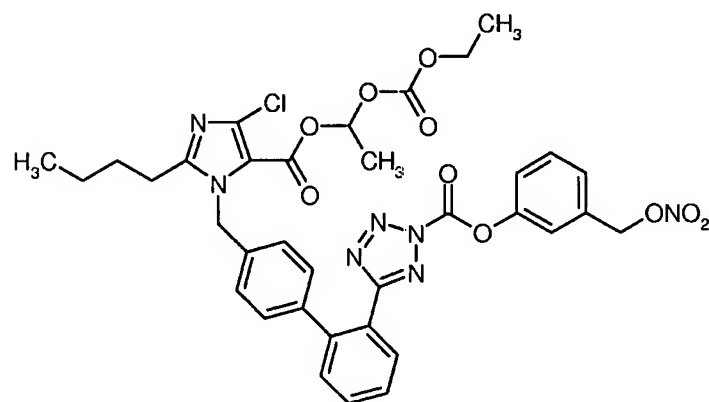
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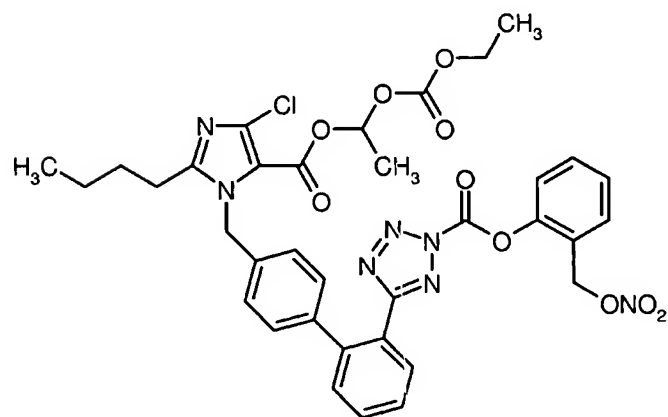
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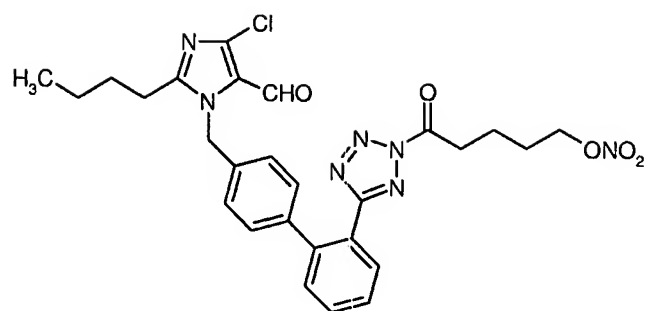
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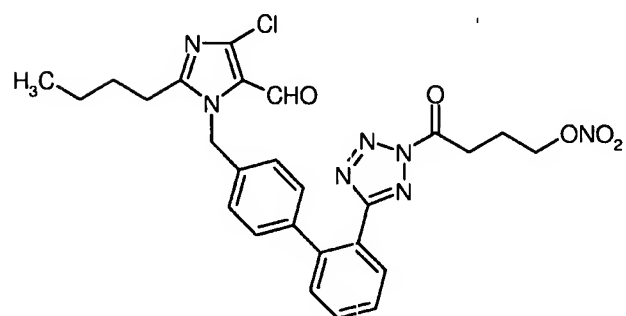
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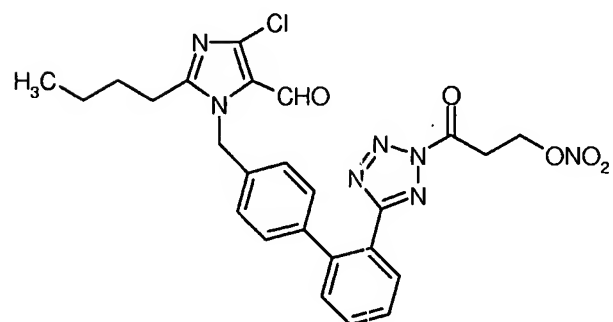
(380)



(381)

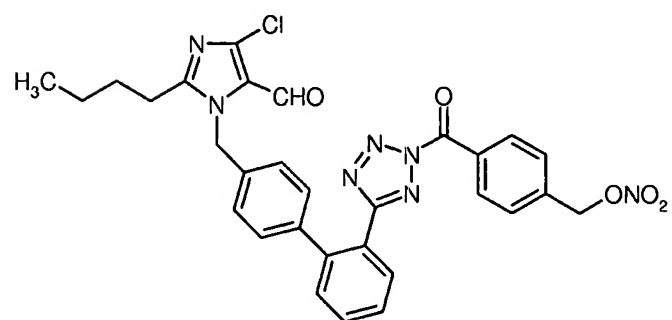


(382)

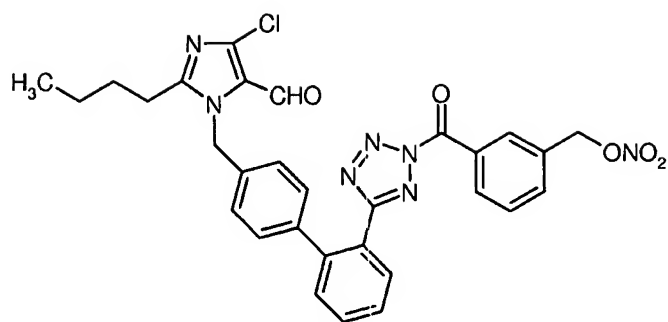


(383)

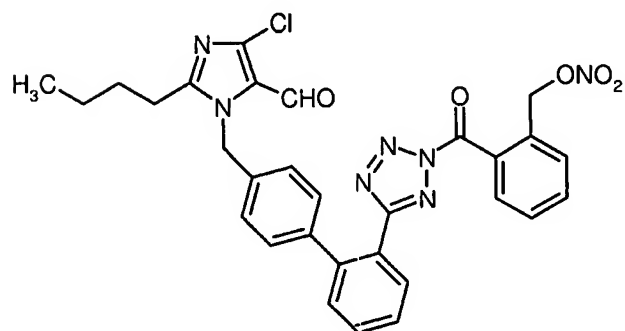
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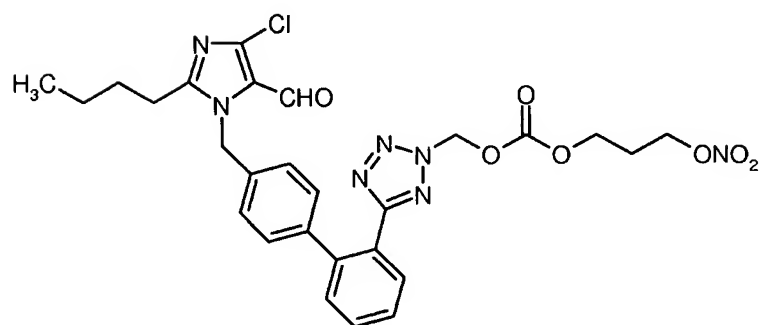
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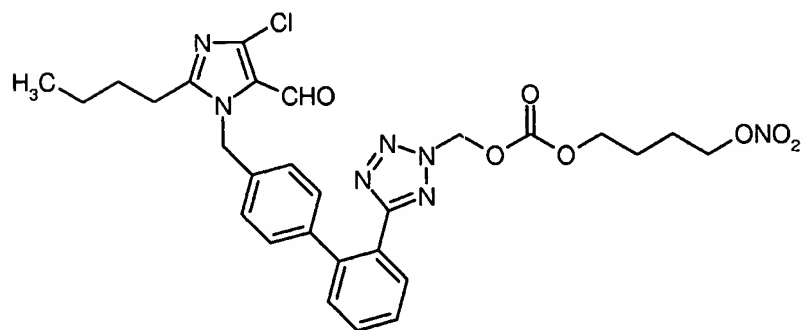
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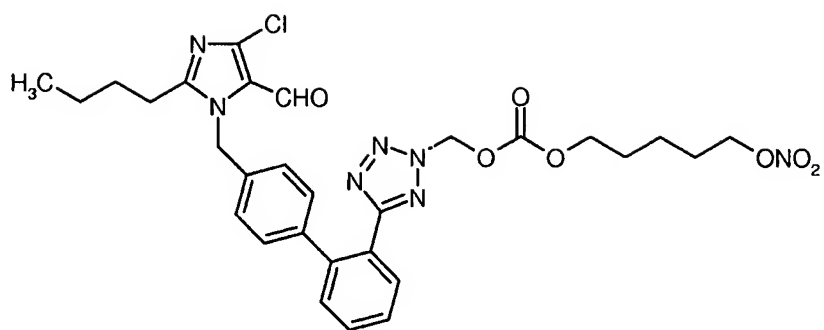
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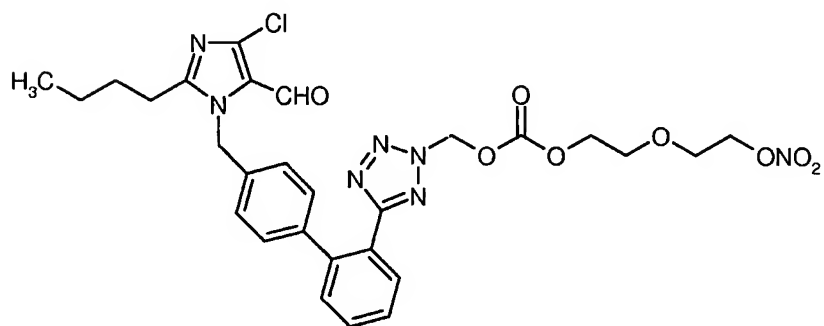
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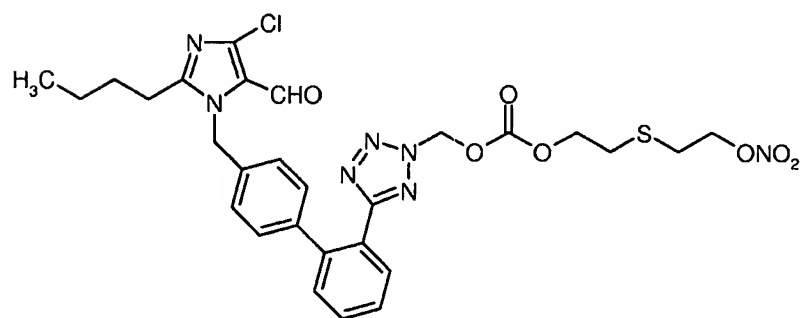
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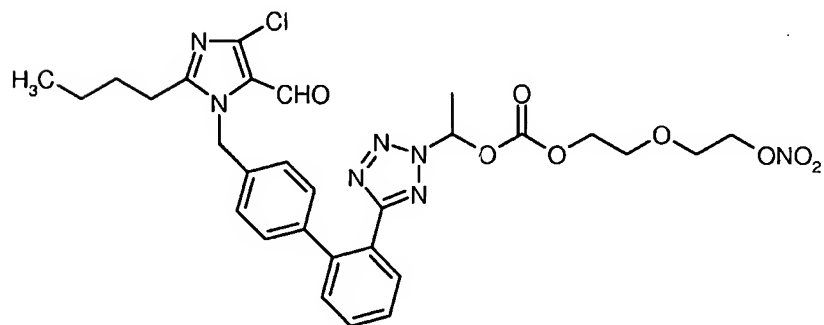
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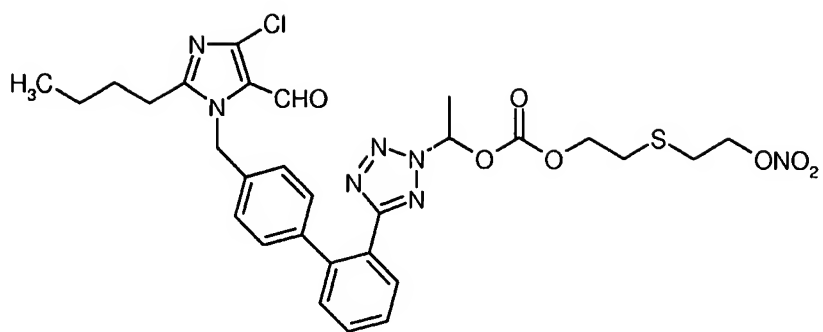
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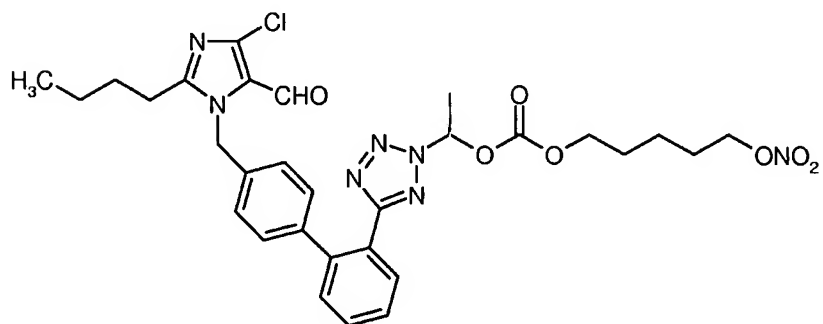
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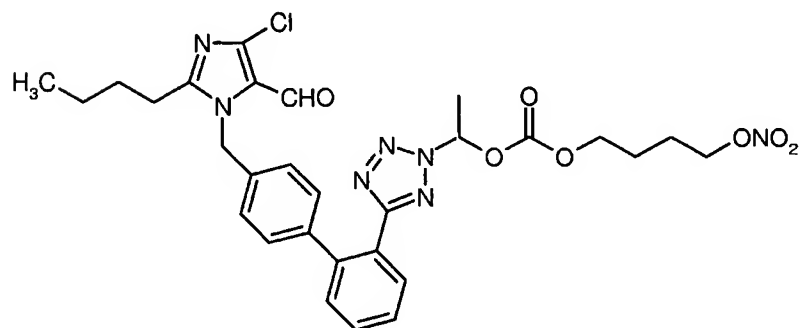
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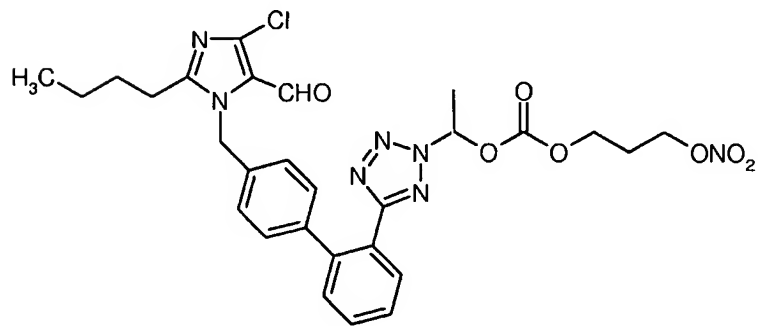
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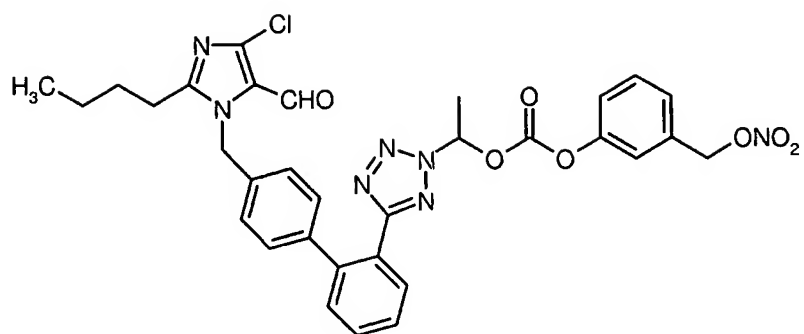
(394)



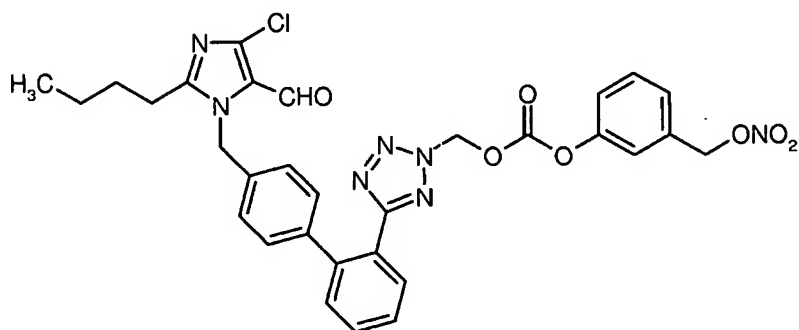
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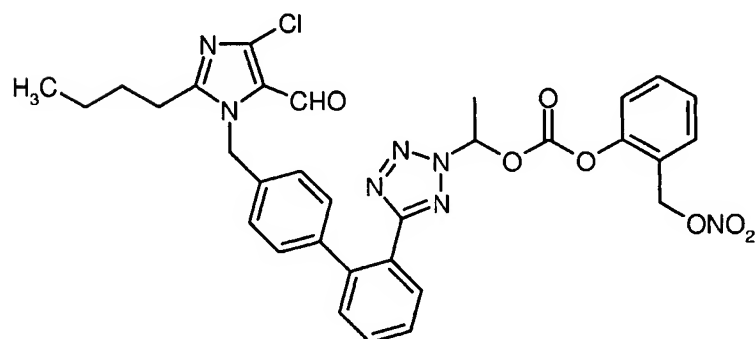
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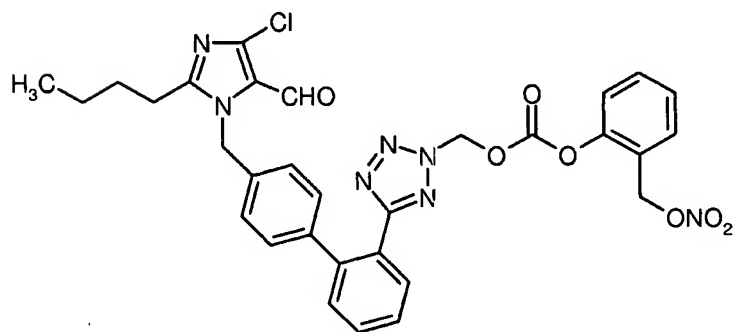
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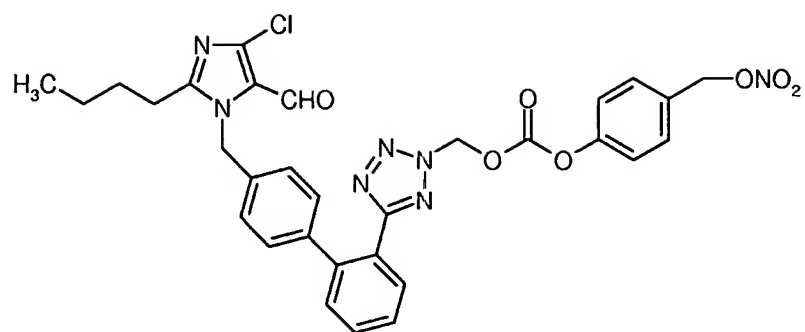
(398)



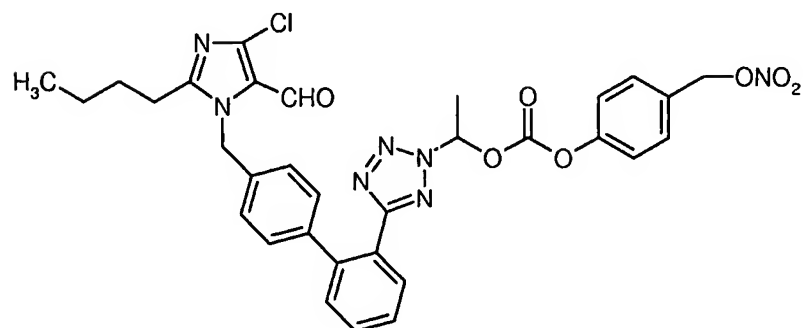
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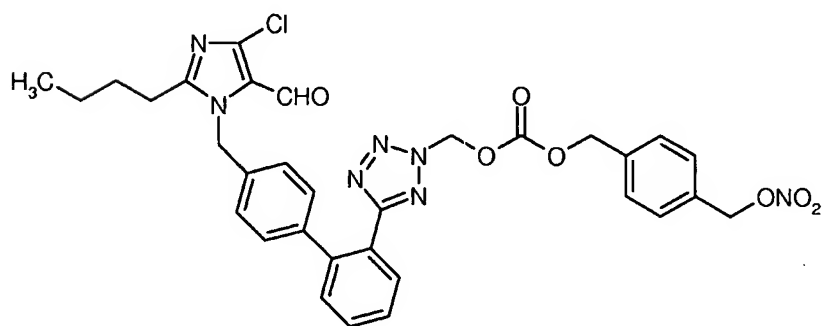
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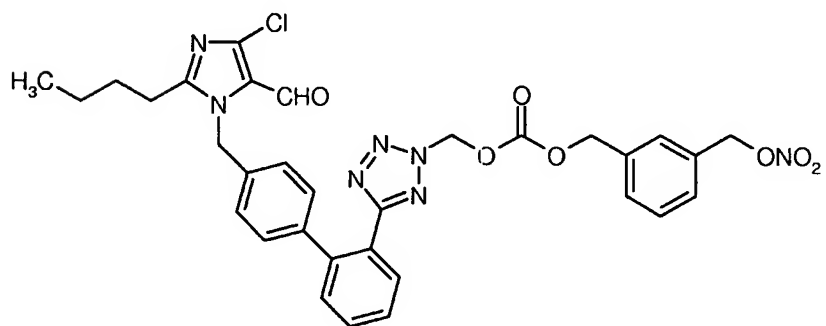
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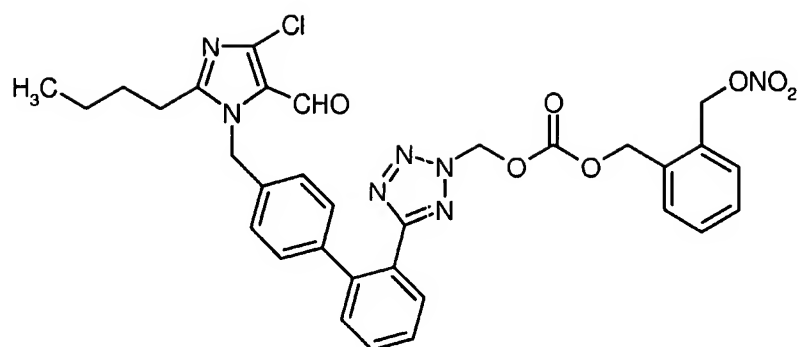
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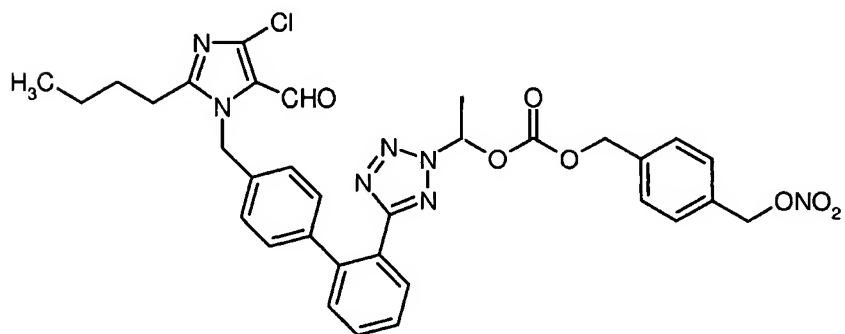
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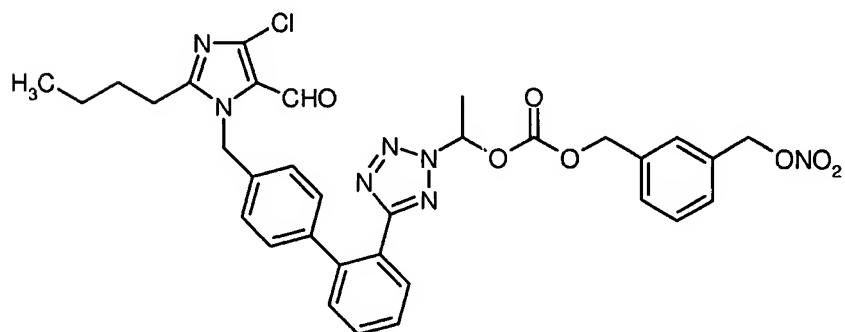
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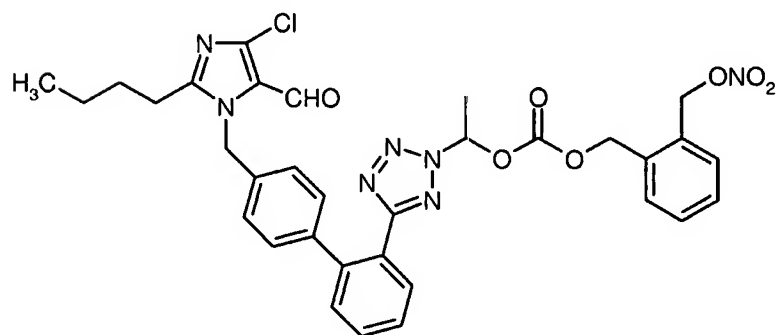
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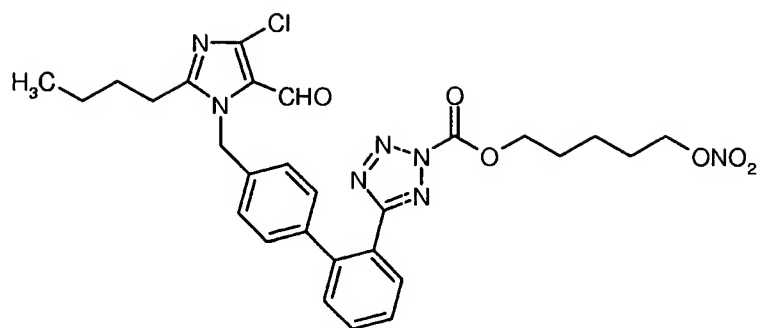
(406)



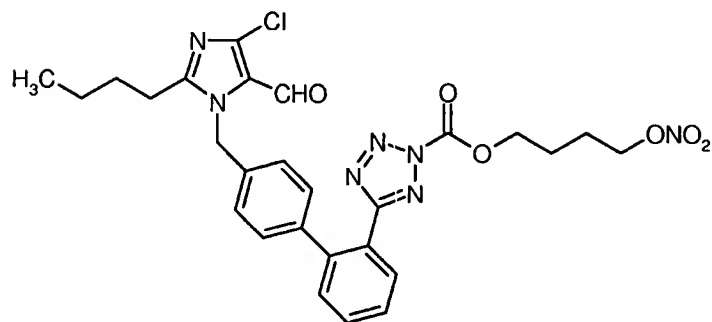
(407)



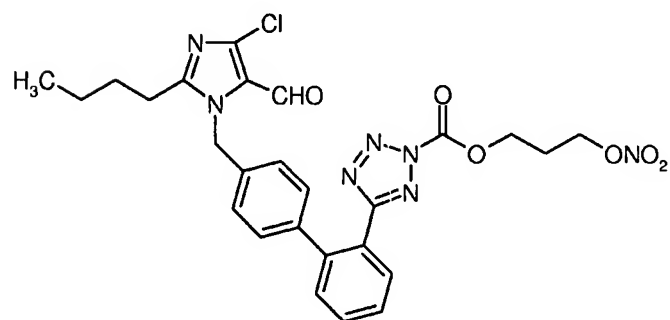
(408)



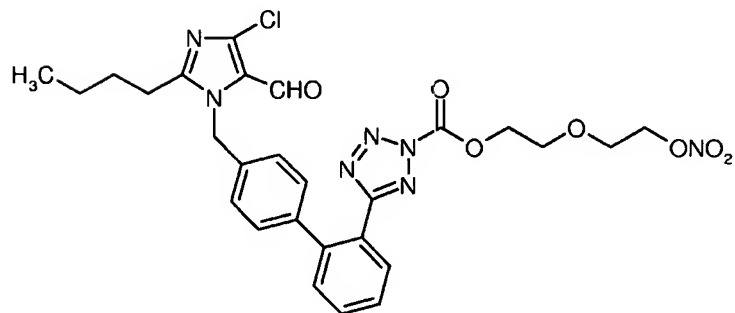
(409)



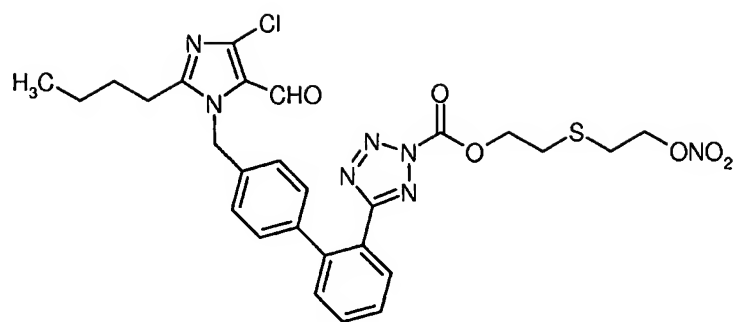
(410)



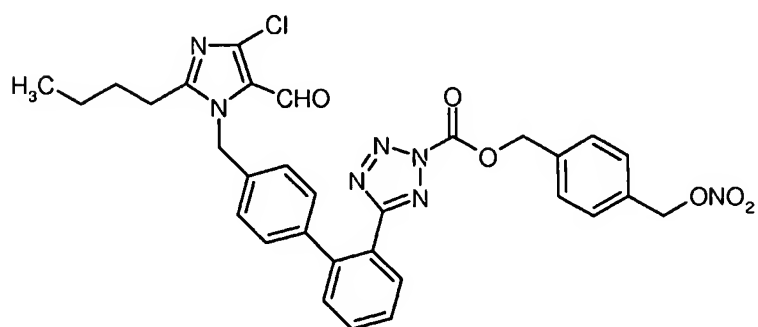
(411)



(412)

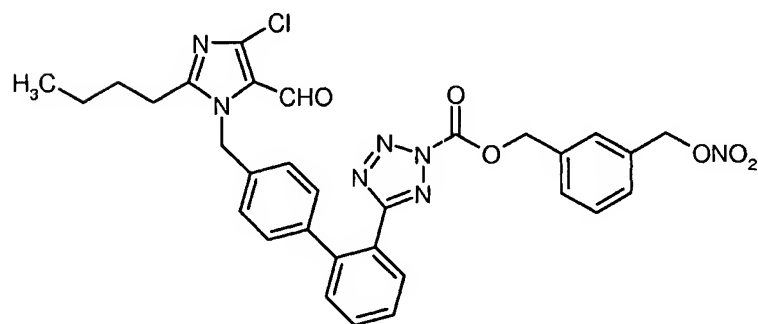


(413)

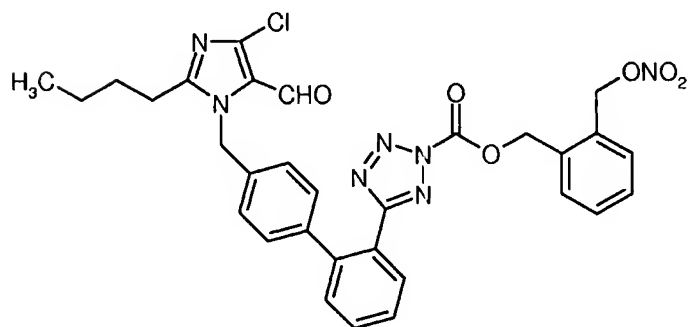


(414)

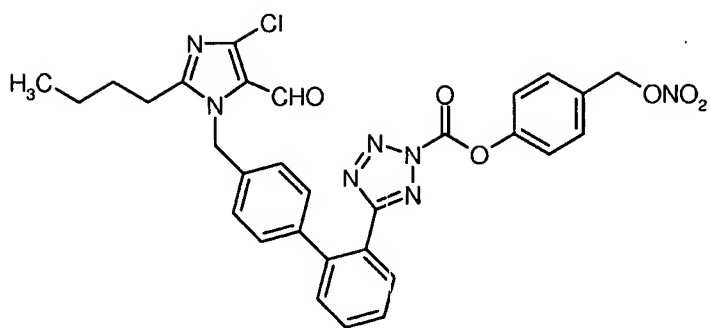
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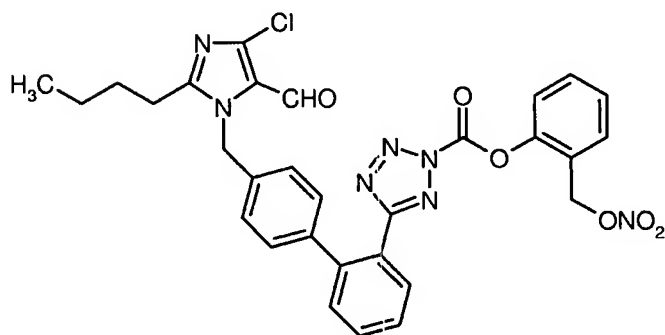
(415)



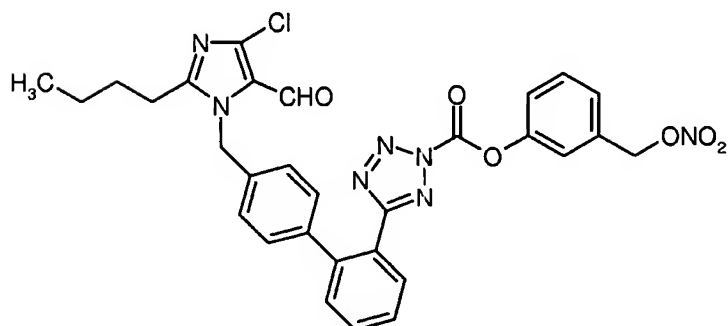
(416)



(417)



(418)

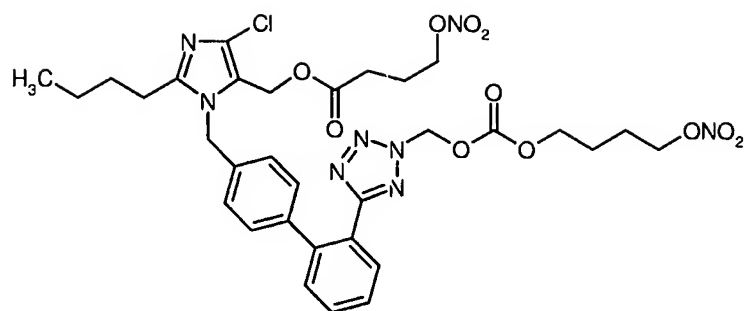


(419)

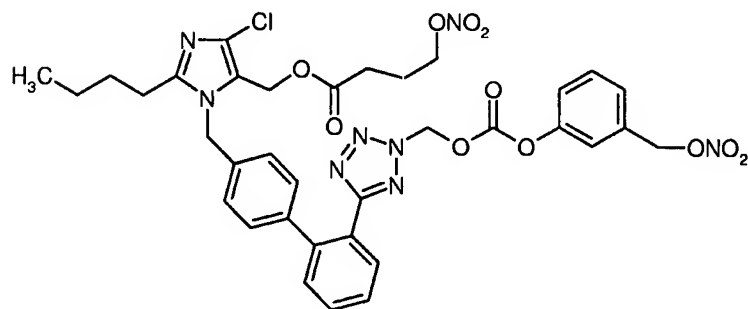
5

13. Compound of formula (I) according to claims 5 and 7
selected from:

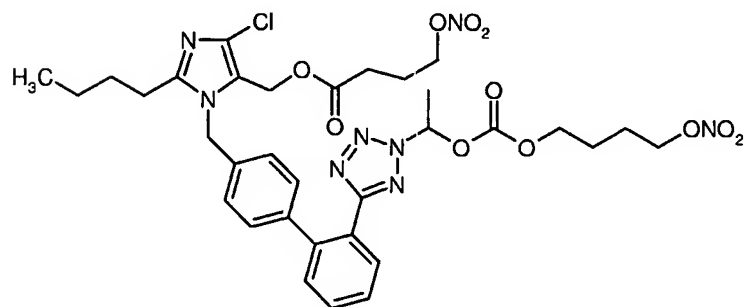
10



(516)



(517)

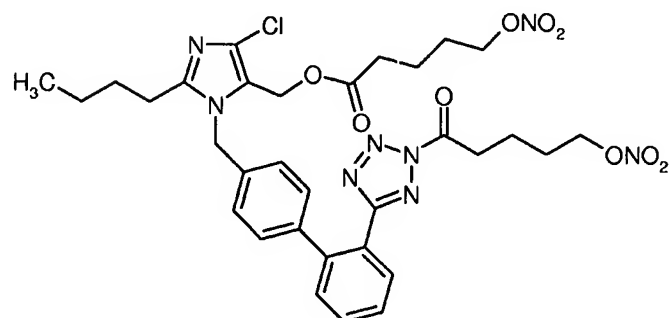


(518)

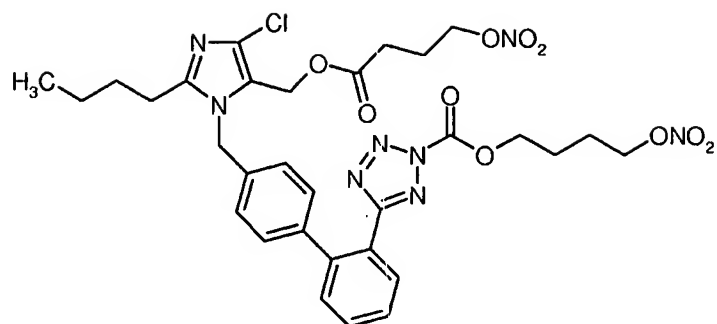
5

14. Compound of formula (I) according to claims 6 and 7
selected from:

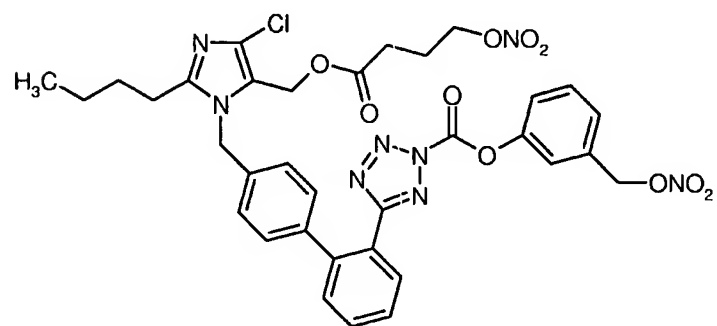
10



(420)

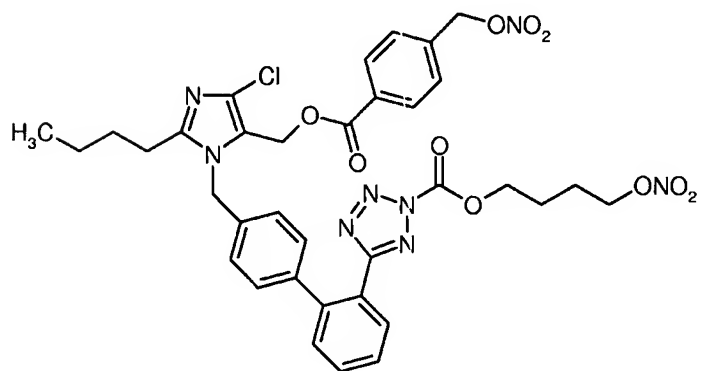


(428)

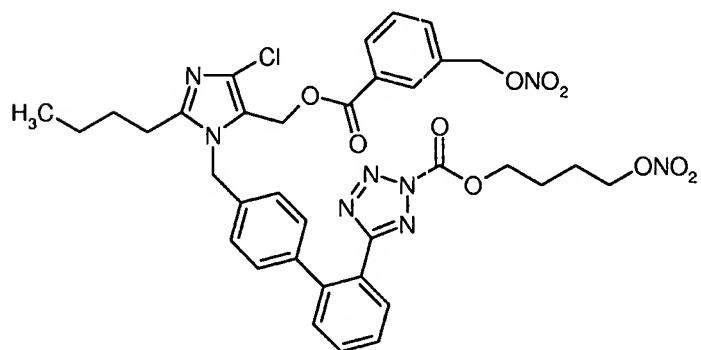


5

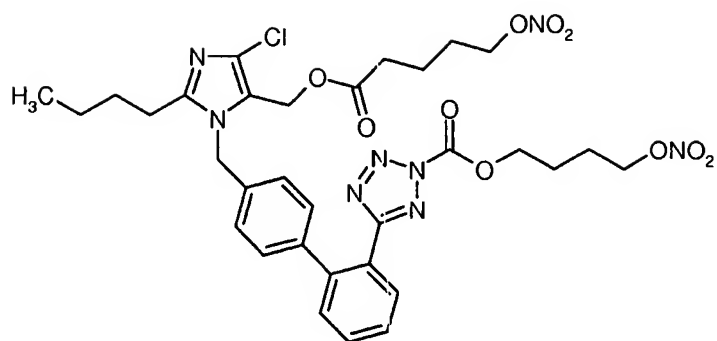
(429)



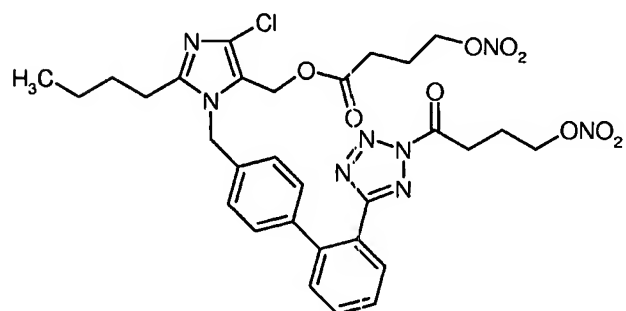
(430)



(431)

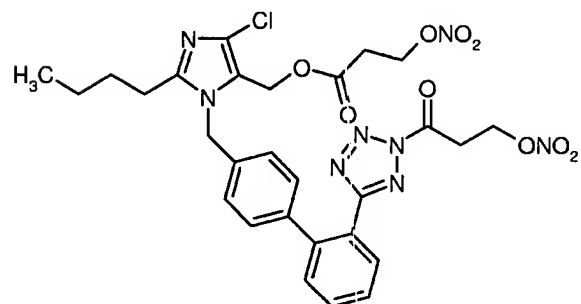


(432)

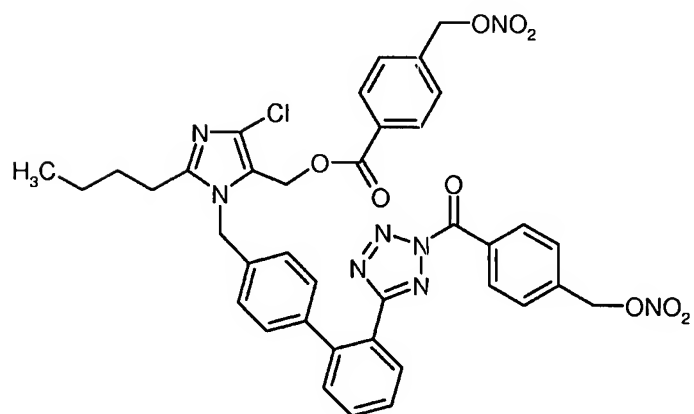


5

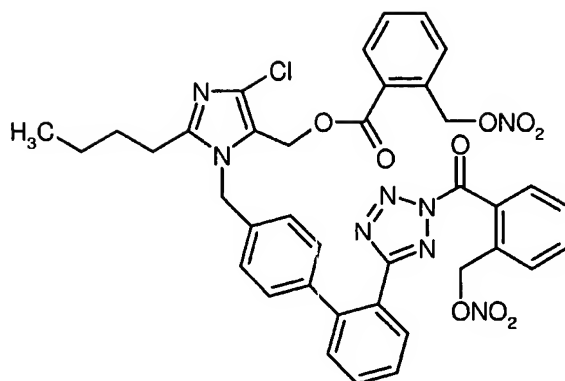
(433)



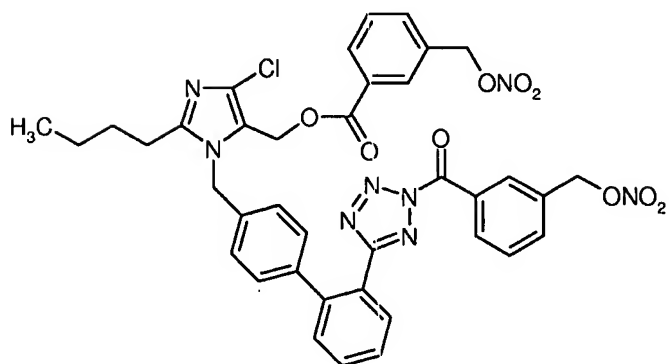
(434)



(435)

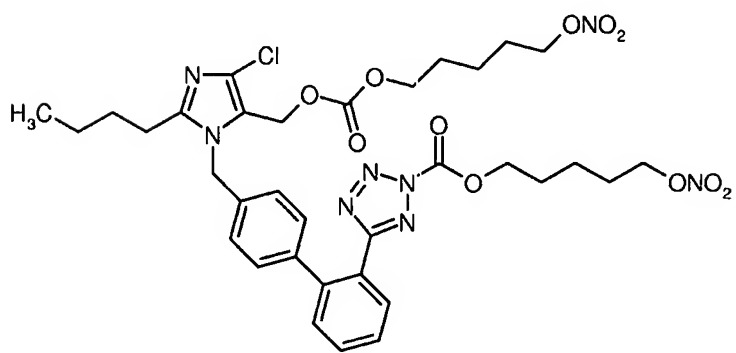


(436)

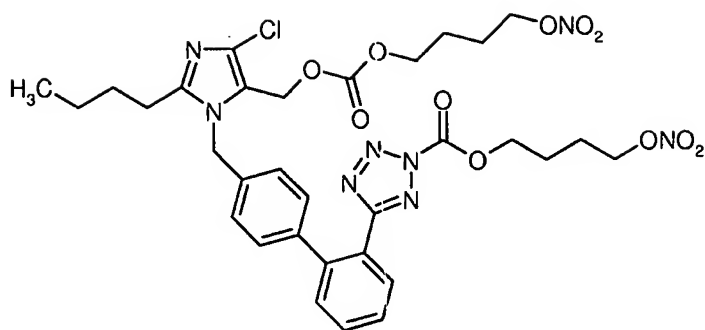


5

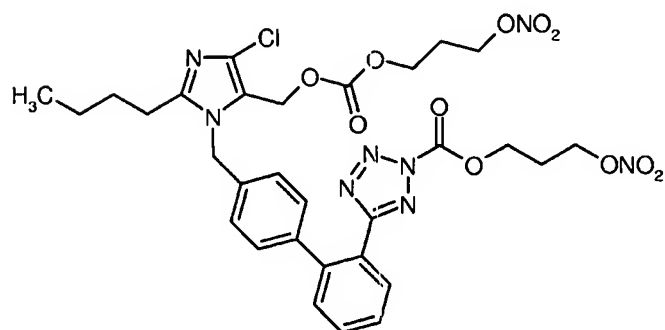
(437)



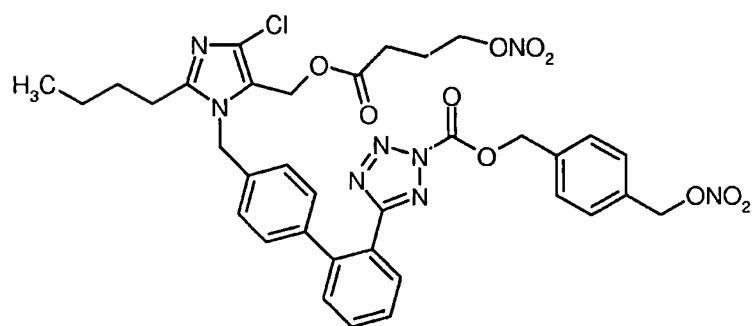
(438)



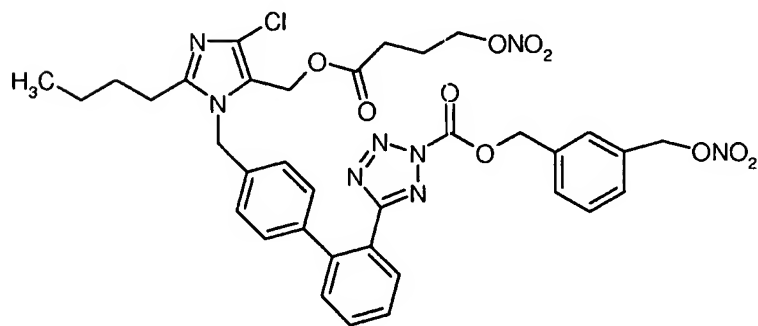
(439)



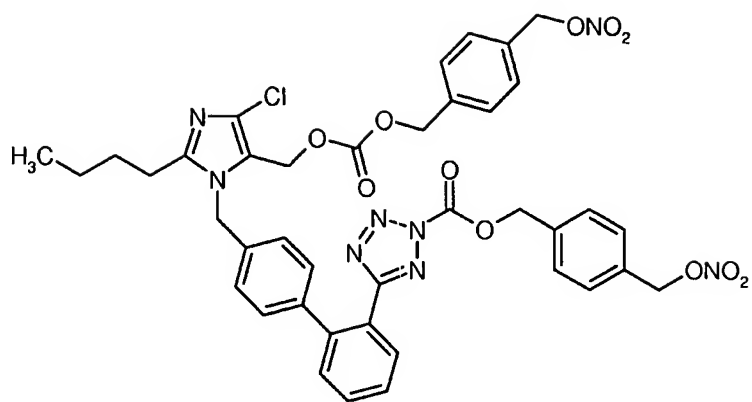
(440)



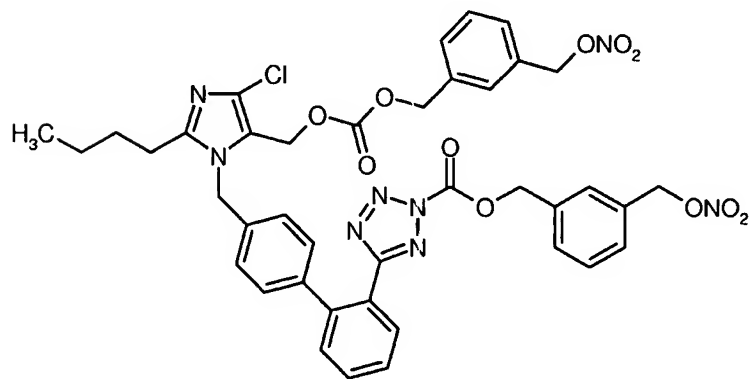
(441)



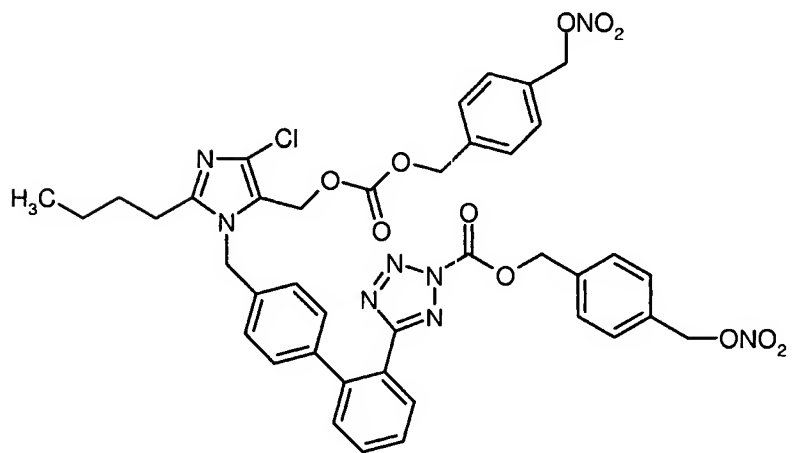
(442)



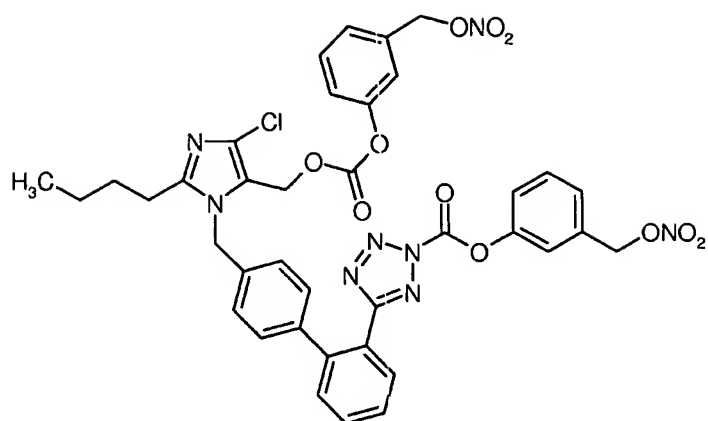
(443)



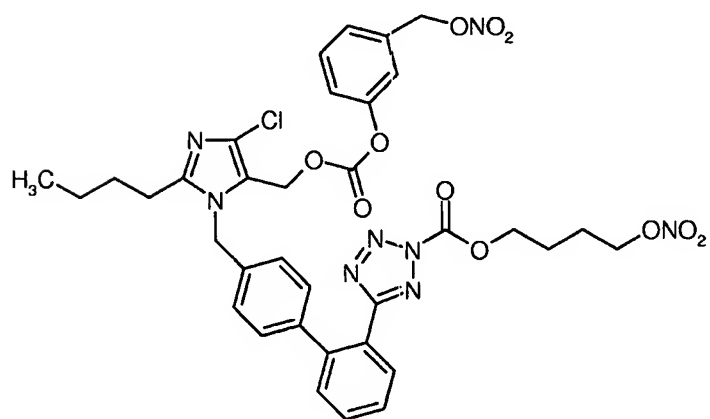
(444)



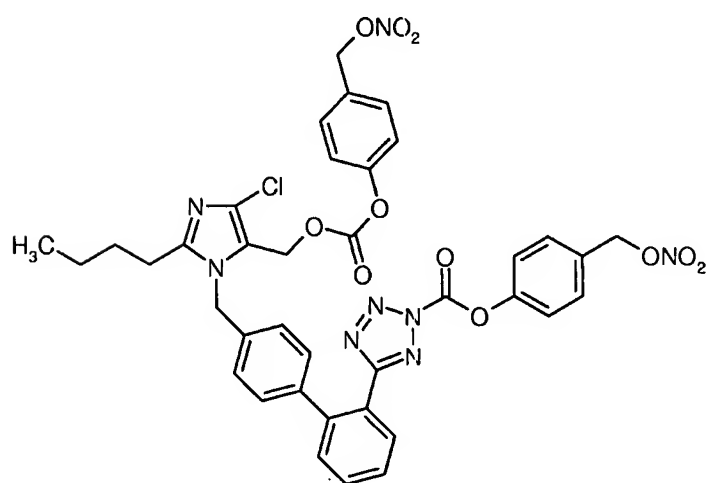
(445)



(446)

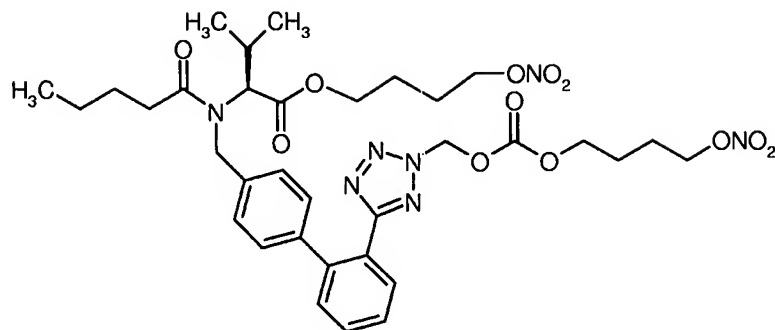


(447)

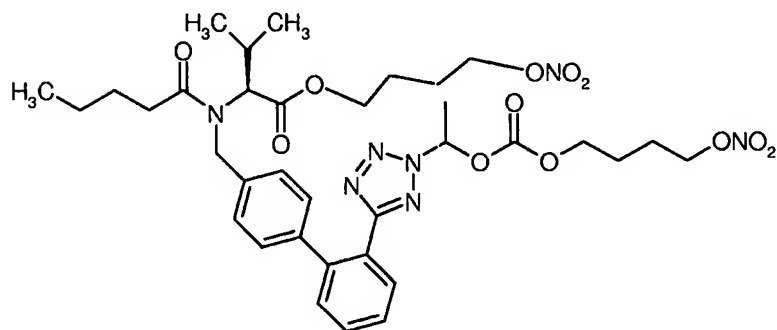


(448)

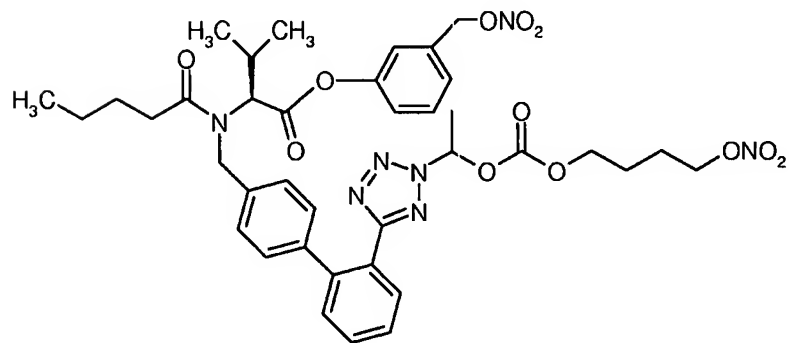
15. Compound of formula (I) according to claims 8 and 11 selected from:



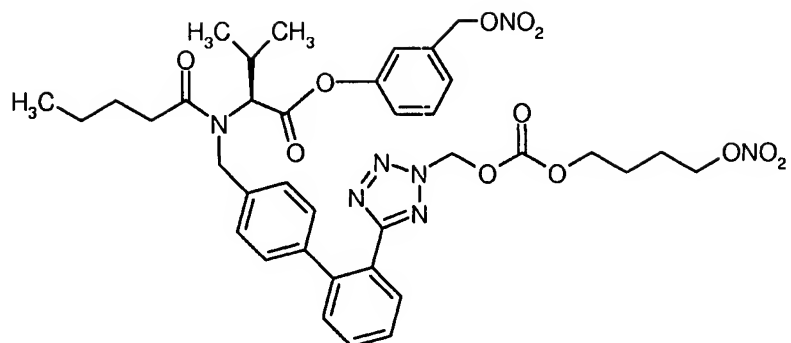
(449)



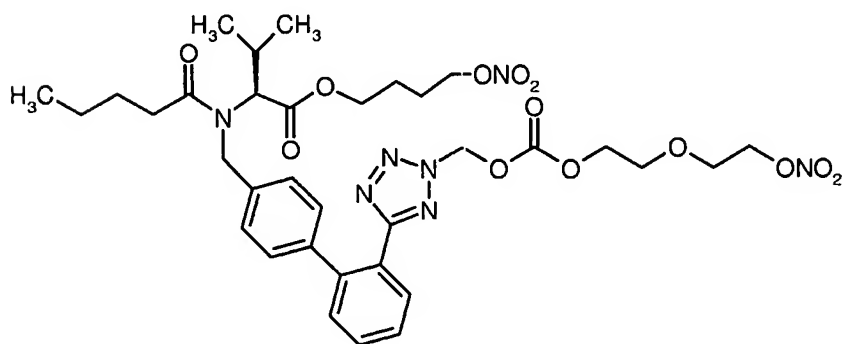
(450)



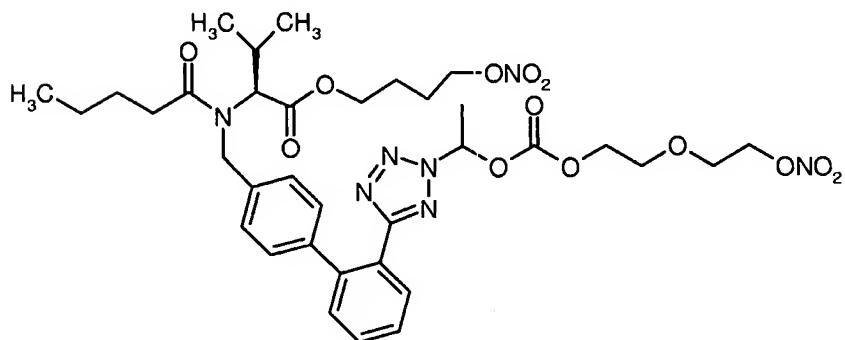
(451)



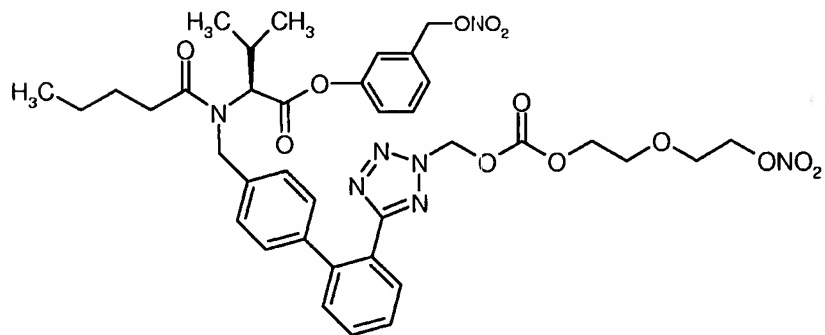
(452)



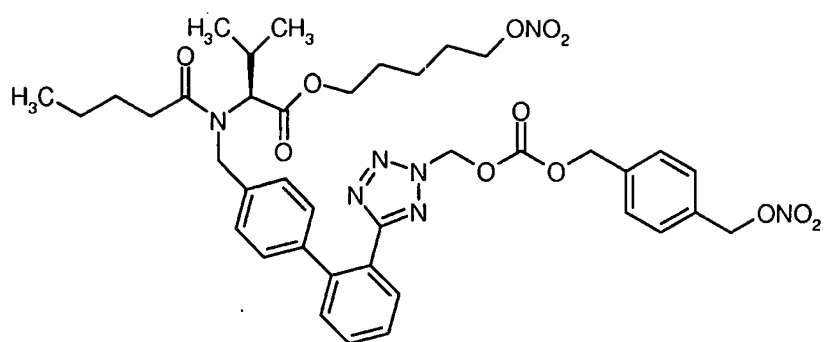
(455)



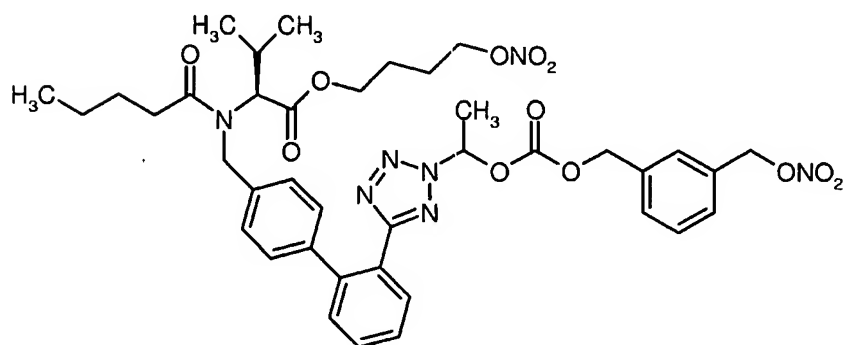
(456)



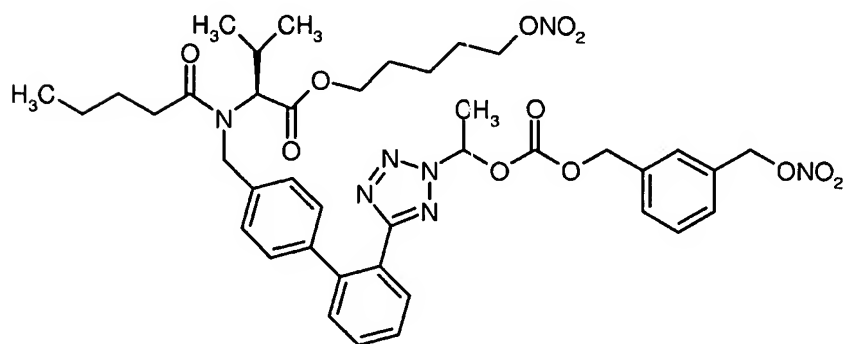
(457)



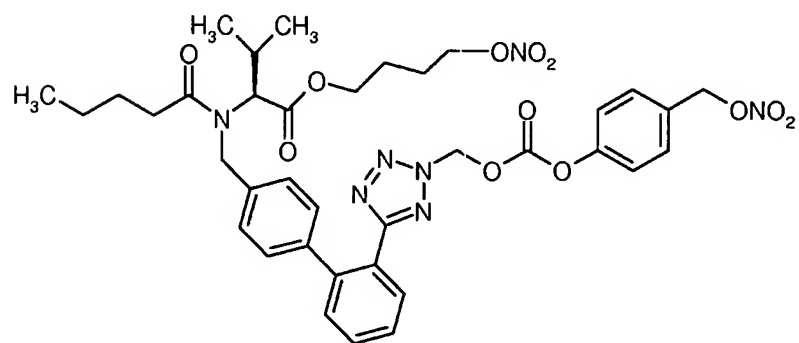
(462)



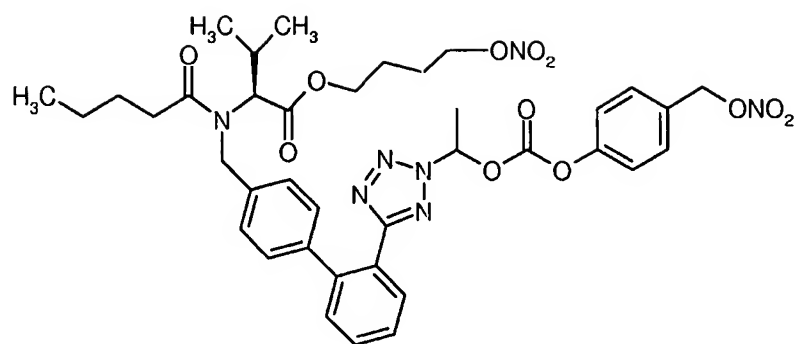
(463)



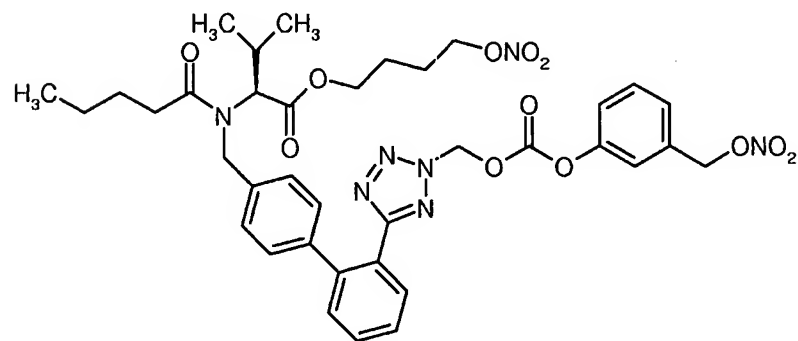
(464)



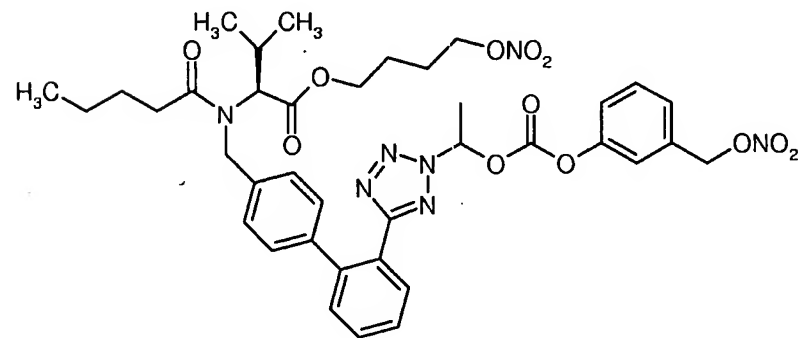
(465)



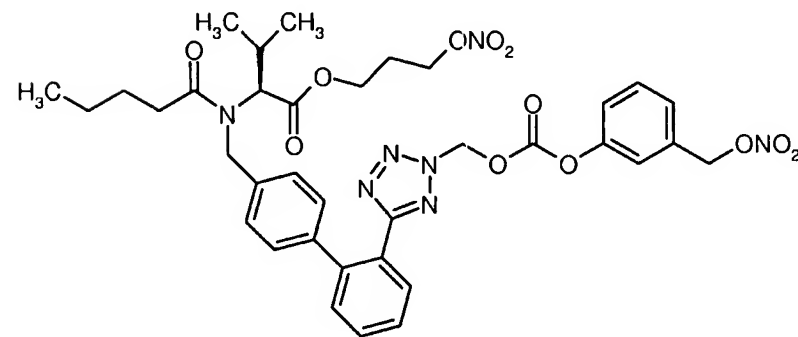
(466)



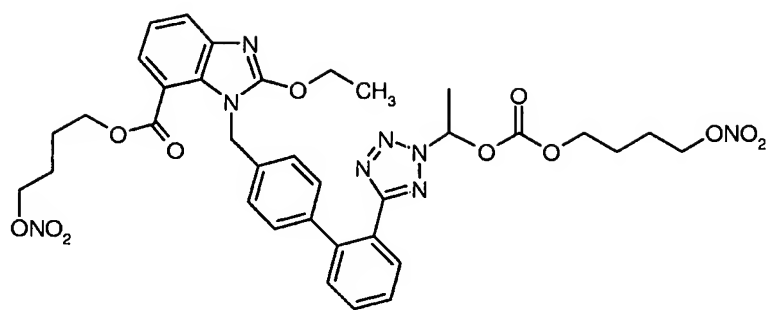
(467)



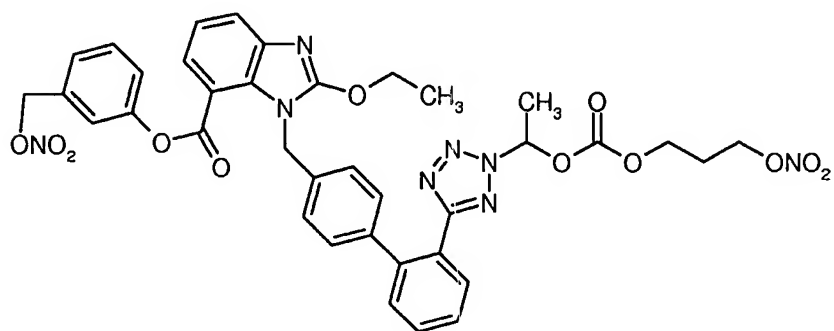
(468)



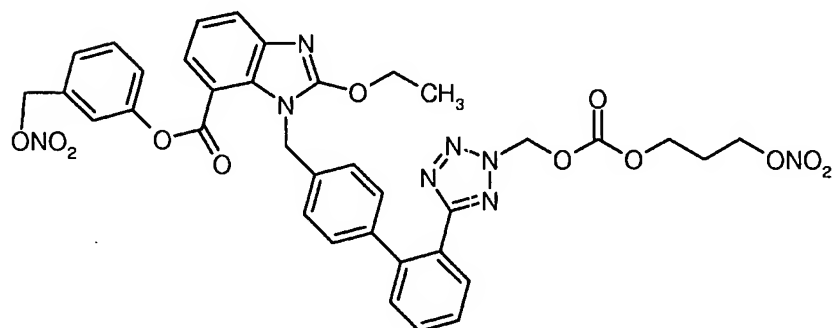
(469)



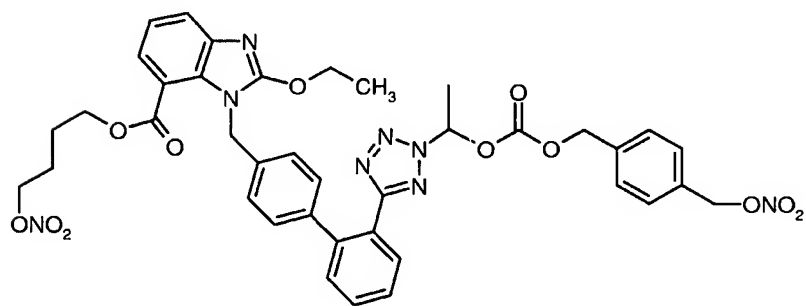
(474)



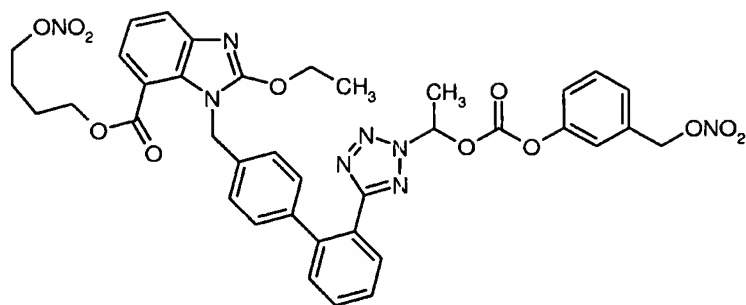
(475)



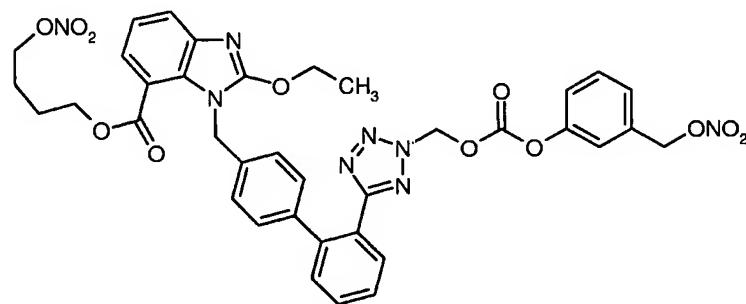
(476)



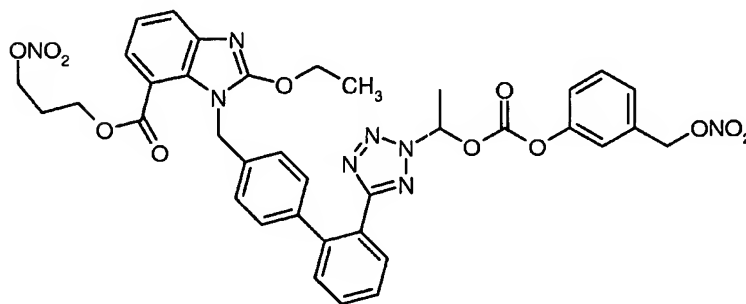
(478)



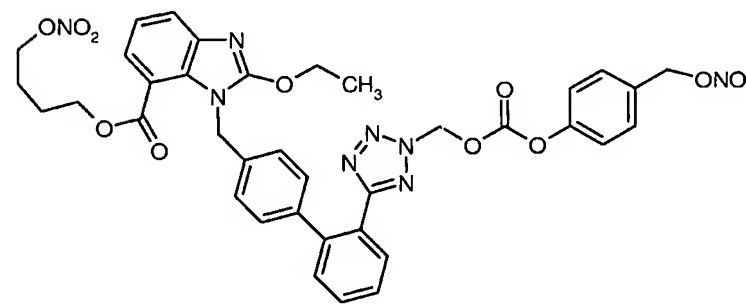
(479)



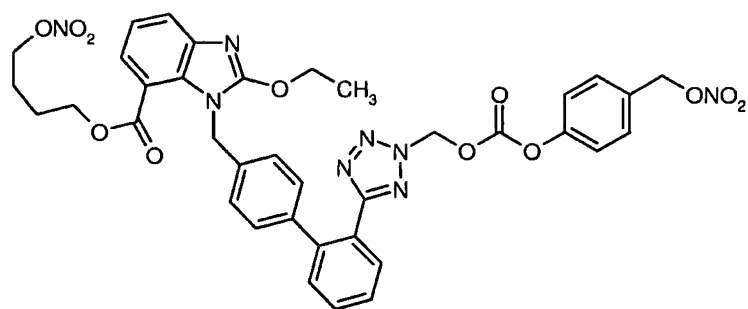
(480)



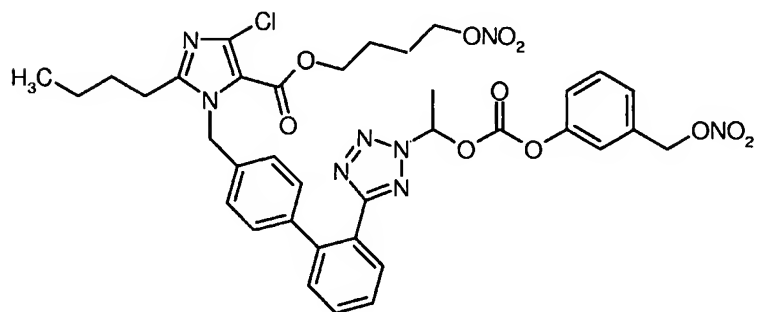
(481)



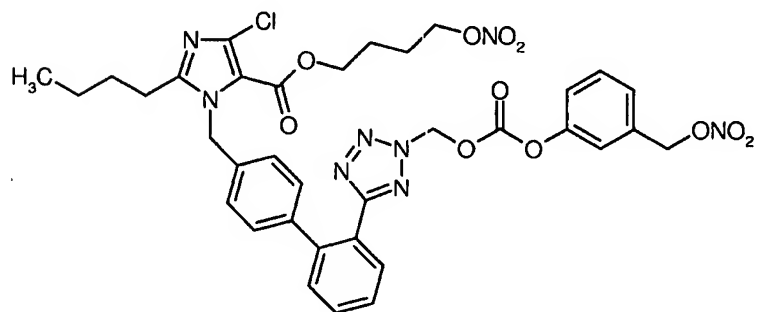
(482)



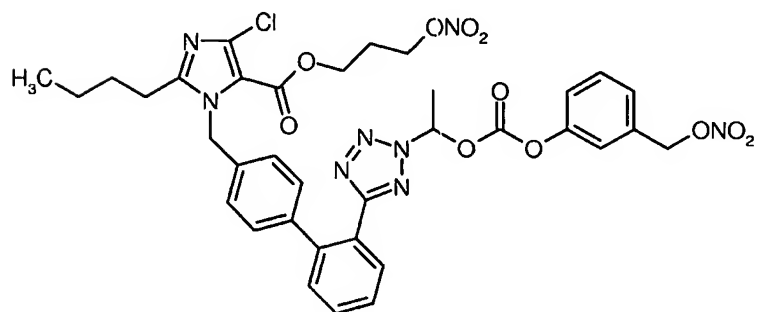
(483)



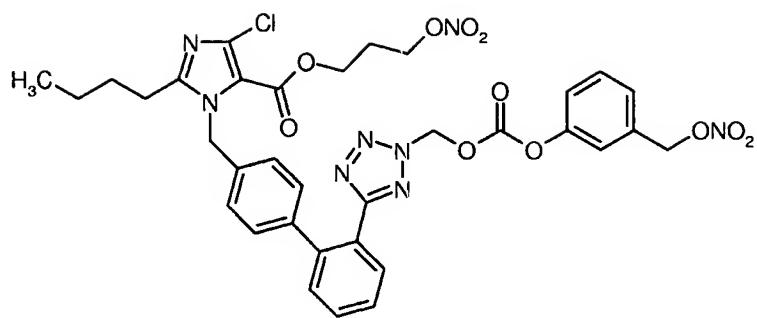
(488)



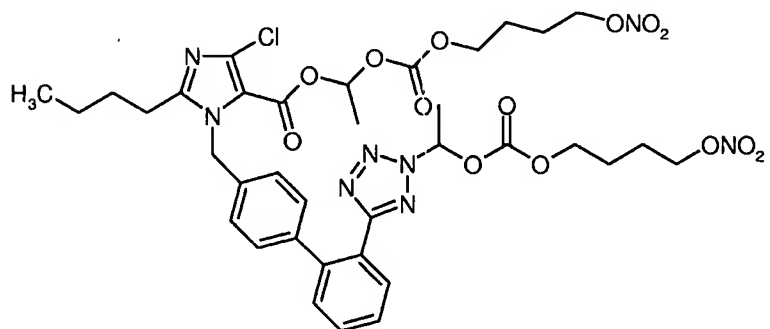
(489)



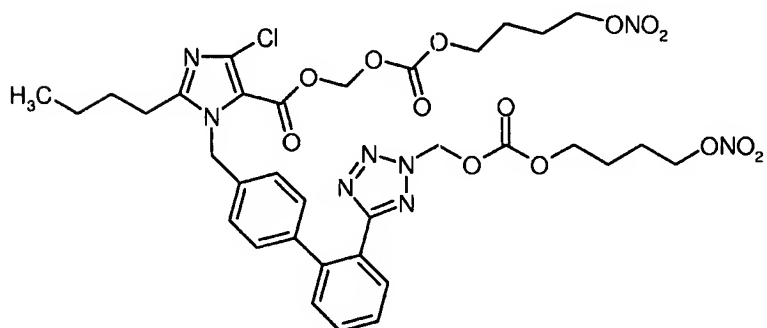
(490)



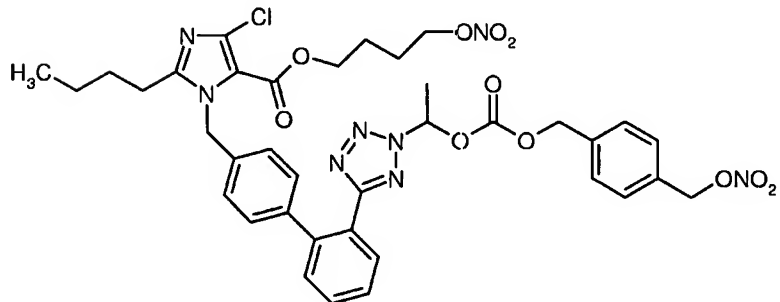
(491)



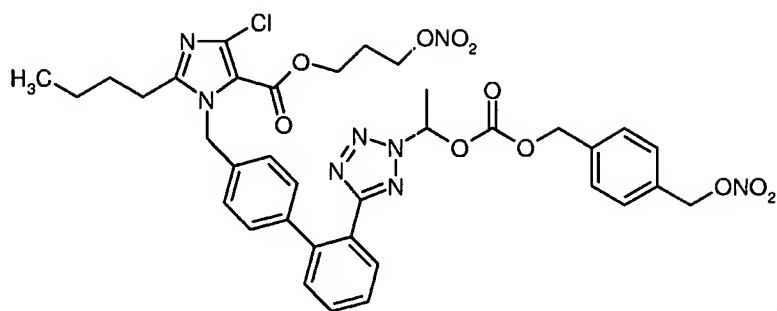
(492)



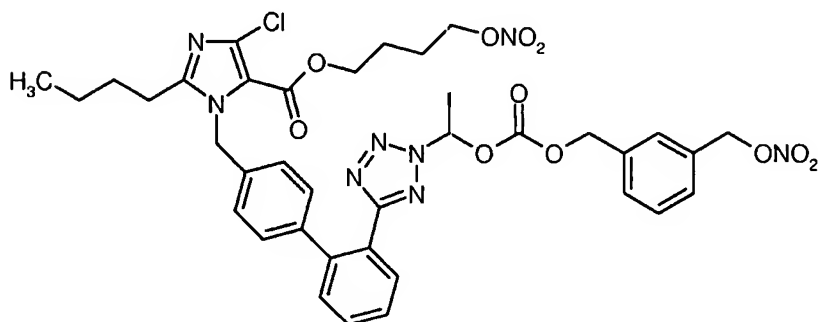
(493)



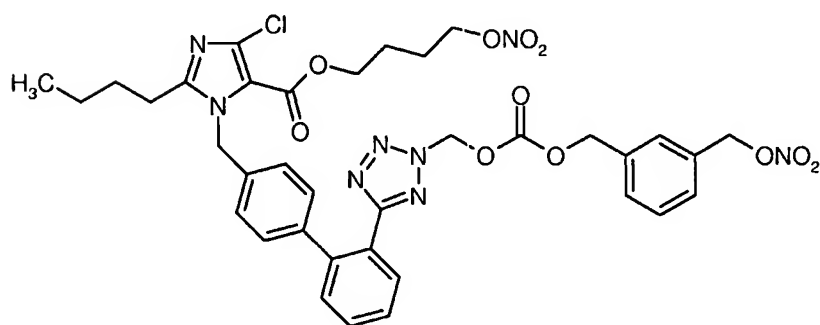
(494)



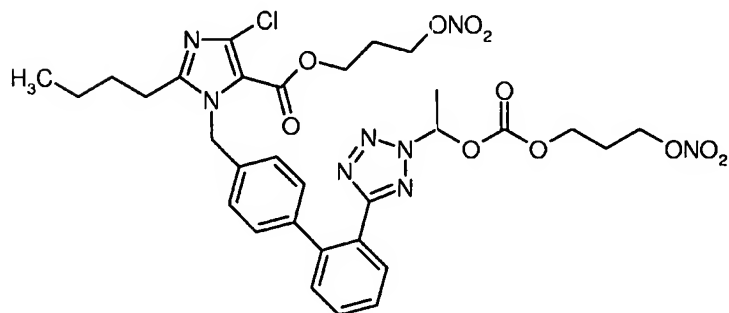
(495)



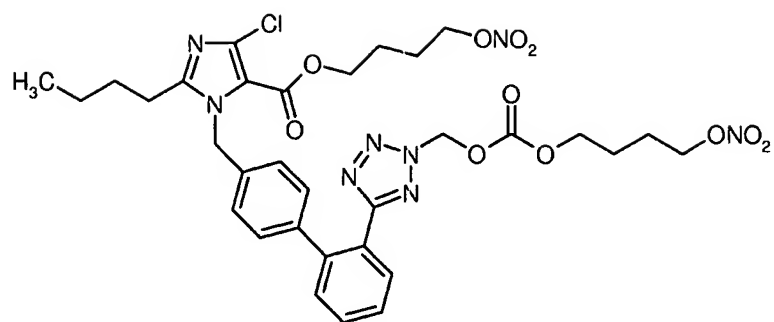
(496)



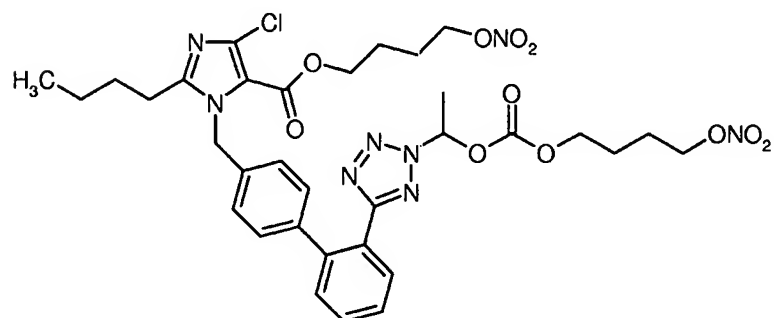
(497)



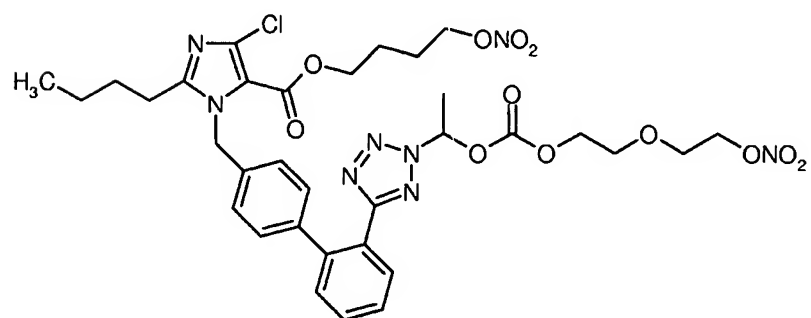
(498)



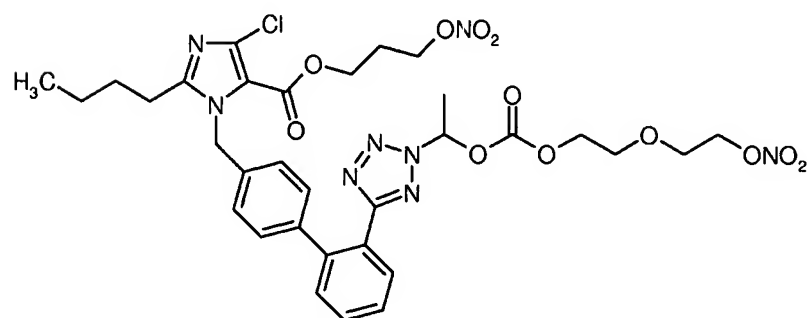
(499)



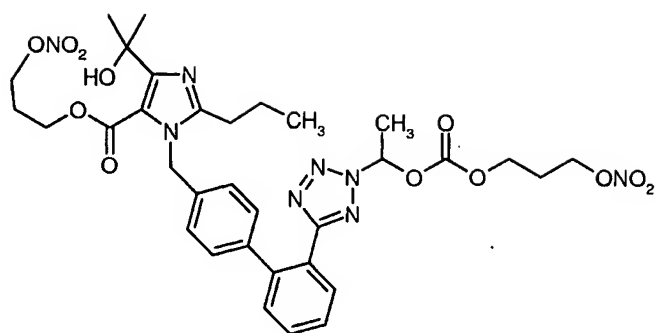
(500)



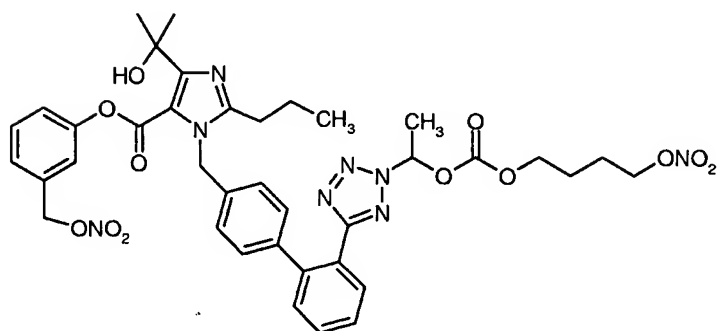
(501)



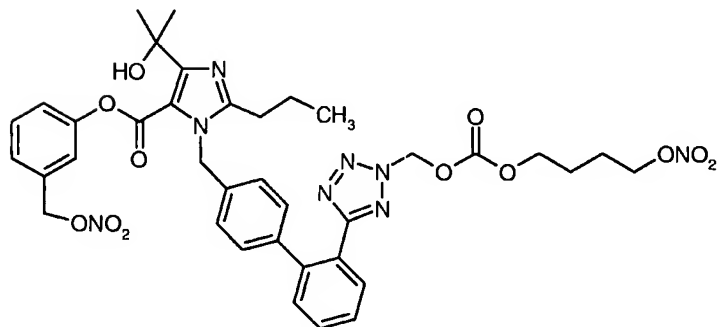
(502)



(507)

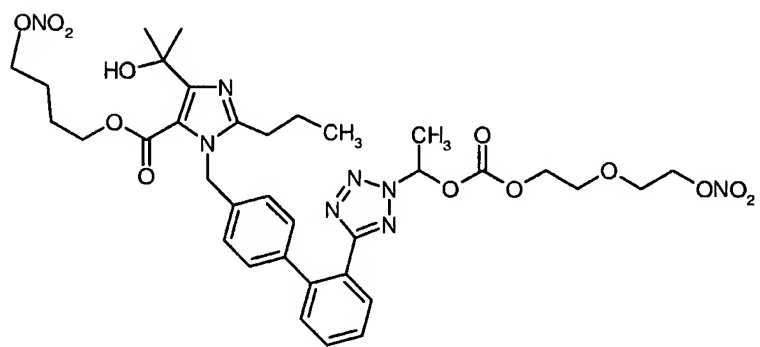


(508)

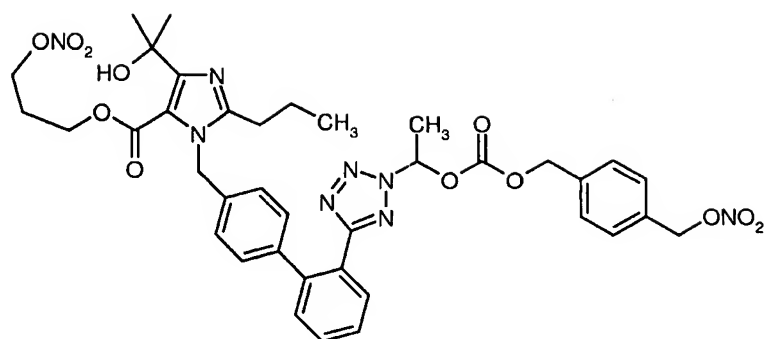


(509)

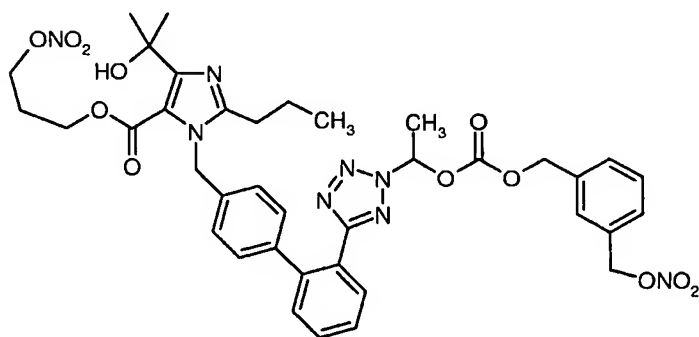
5



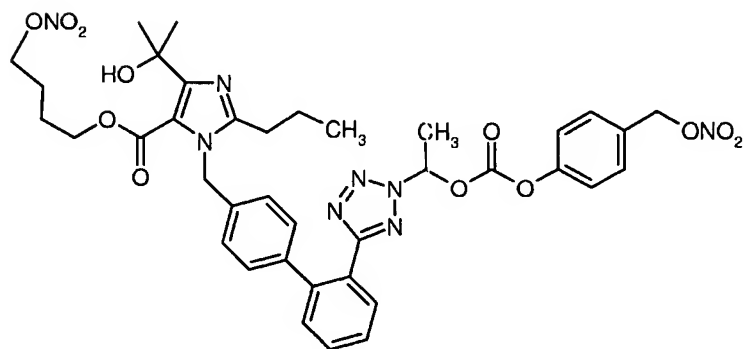
(510)



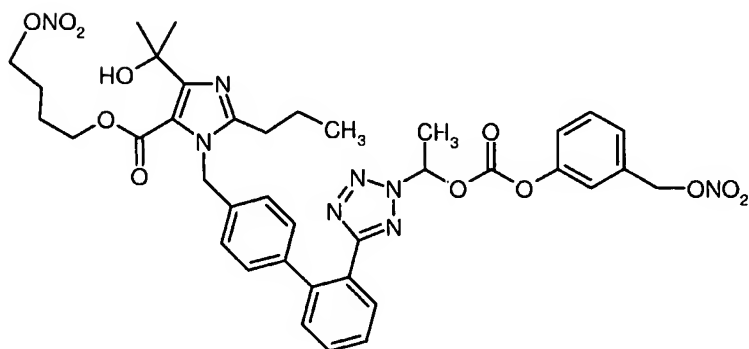
(512)



(513)

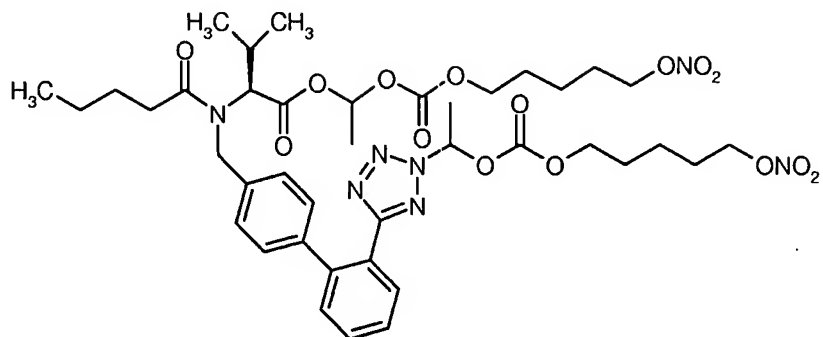


(514)



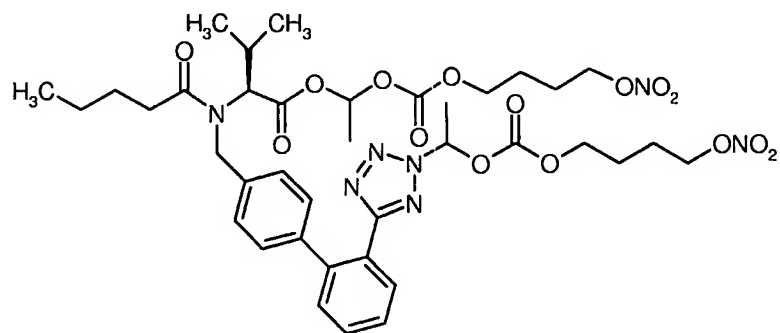
(515)

16. Compound of formula (I) according to claims 10 and 11 selected from:

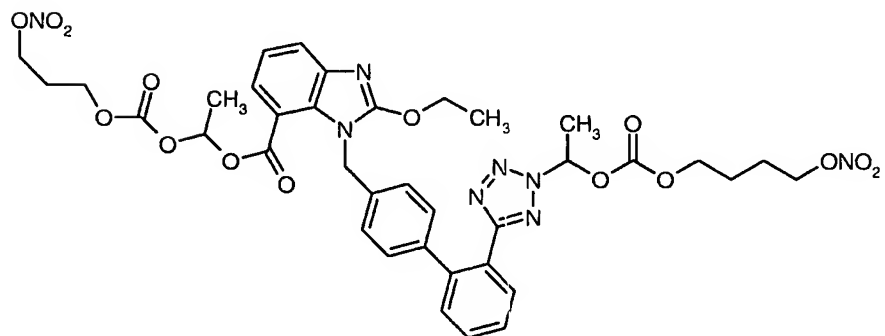


5

(453)

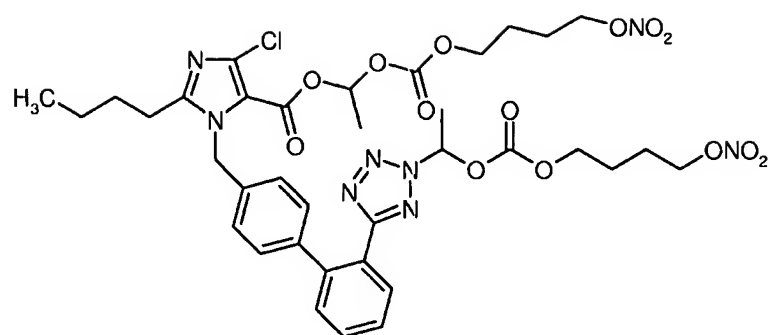


(454)

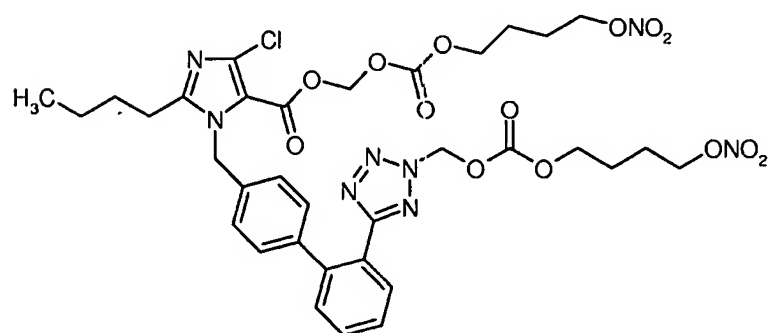


10

(477)

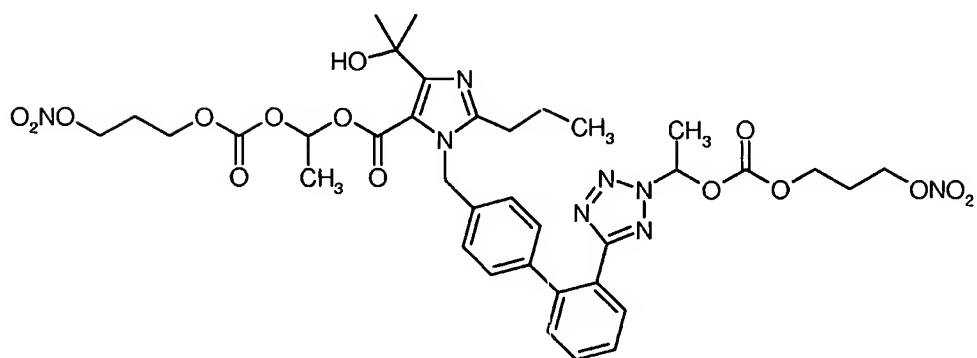


(492)



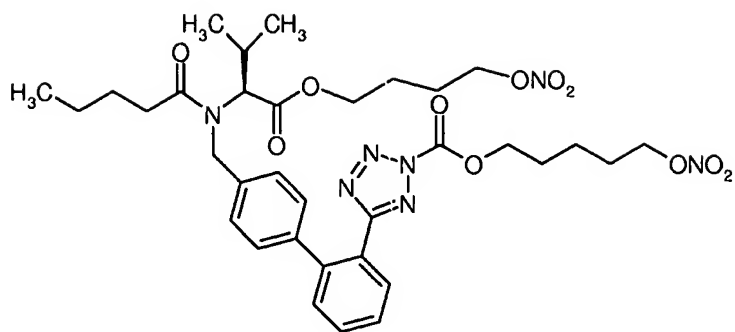
(493)

5

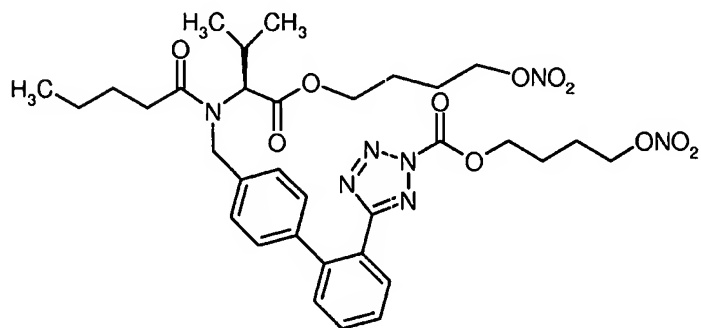


(511)

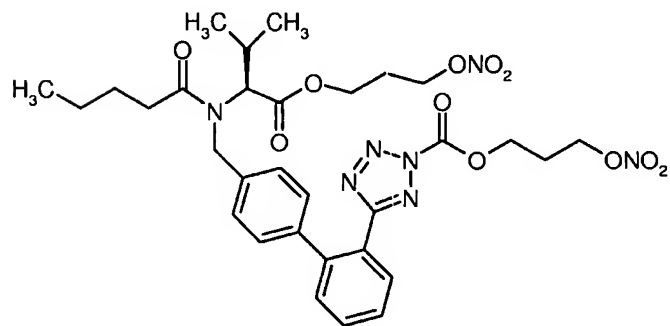
17. Compound of formula (I) according to claims 9 and 11
 10 selected from



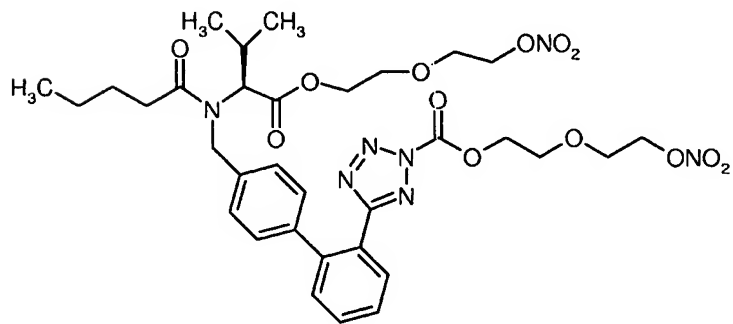
(421)



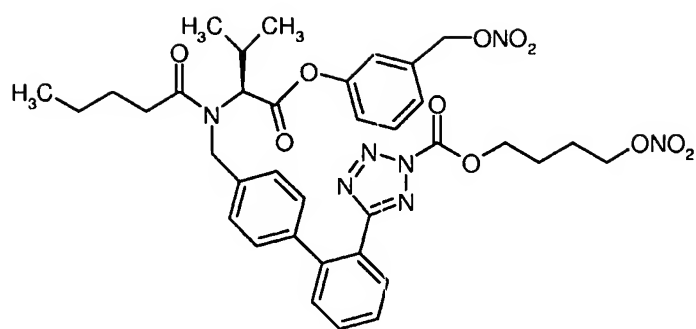
(422)



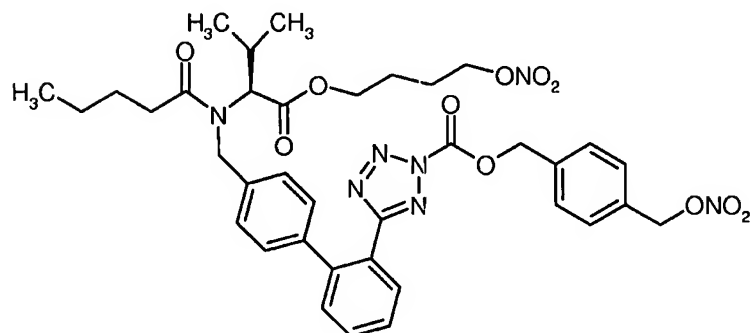
(423)



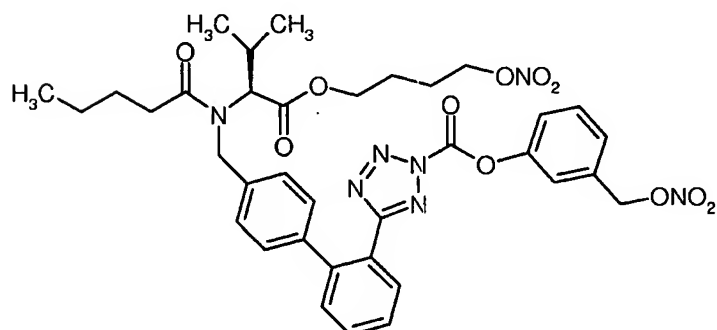
(424)



(425)



(426)



(427)

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18. Compounds of formula (I) according to claims 1 to 17
for use as medicaments.

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19. Use of compound of formula (I) according to claims 1 to 17, for the manufacture of a medicament for treatment or prophylaxis of cardiovascular, renal and chronic liver diseases, inflammatory processes and metabolic syndromes.

20. Use of a compound of formula (I) according to claims 1 to 17 for the manufacture of a medicament for treatment or prophylaxis of heart failure, myocardial infarction, ischemic stroke, atherosclerosis, ocular and pulmonary hypertension, hypertension, diabetic nephropathy, peripheral vascular diseases, left ventricular dysfunction and hypertrophy, liver fibrosis and portal hypertension.
- 10 21. Use of a compound according to claims 1 to 17 for the manufacture of a medicament having antithrombotic and antiplatelet activity.
- 15 22. A pharmaceutical composition comprising a compound of general formula (I) or a salt or stereoisomer thereof according to claims 1 to 17 and pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/050348

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07D257/04 A61P9/12	C07D403/10 A61P7/02
	C07D405/14	C07D471/04 A61P9/04
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C07D A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BRESCHI ET AL: "NO-Sartans: A New Class of Pharmacodynamic Hybrids as Cardiovascular Drugs" JOURNAL OF MEDICINAL CHEMISTRY, vol. 47, no. 23, 2004, page 5597-5600, XP002374434 cited in the application the whole document	1-22
A	WO 99/67231 A (NICOX SA) 29 December 1999 (1999-12-29) the whole document	1-22
P,A	WO 2005/011646 A (NICOX SA) 10 February 2005 (2005-02-10) the whole document	1-22
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
A document defining the general state of the art which is not considered to be of particular relevance		
E earlier document but published on or after the international filing date		
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		
T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention		
X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone		
Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art		
Z document member of the same patent family		
Date of the actual completion of the international search 28 March 2006		Date of mailing of the international search report 13/04/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Cortés, J

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/050348

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>BRESCHI ET AL: "New NO-Releasing Pharmacodynamic Hybrids of Losartan and Its Active Metabolite: Design, Synthesis, and Biopharmacological Properties" JOURNAL OF MEDICINAL CHEMISTRY, ASAP, 22 March 2006 (2006-03-22), pages A-I, XP002374461 published on Web DOI: 10.1021/jm0600186 the whole document</p> <p>-----</p>	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/050348

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